Original research

What predicts poor outcome after successful thrombectomy in late time windows?

Jeremy J Heit ,[1] Michael Mlynash,[2] Soren Christensen,[2] Stephanie M Kemp,[2] Maarten G Lansberg,[2] Michael P Marks,[1] Jean-Marc Olivot ,[3] Albers W Gregory[2]

[1]Department of Radiology, Stanford University, Stanford, California, USA
[2]Department of Neurology, Stanford University, Stanford, California, USA
[3]Vascular Neurology, Stroke Department, Toulouse University Hospital, Toulouse, France

Correspondence to
Dr Jeremy J Heit, Department of Radiology, Stanford University, Stanford CA 94305, California, USA; jheit@stanford.edu

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ABSTRACT

Background Thrombectomy for acute ischemic stroke treatment leads to improved outcomes, but many patients do not achieve a good outcome despite successful reperfusion. We determined predictors of poor outcome after successful thrombectomy (TICI 2b–3) with an emphasis on modifiable factors.

Methods Patients from the randomized DEFUSE 3 trial who underwent thrombectomy with TICI 2b–3 revascularization were included. Primary outcome was a poor outcome at 90 days (modified Rankin Scale score 3–6).

Results 70 patients were included. Poor outcome patients were older (73.5 vs 66.5 years; P=0.01), more likely to be female (68% vs 39%; P=0.02), had higher NIHSS scores (20 vs 13; P<0.001), and had poor cerebral perfusion collaterals (hypoperfusion intensity ratio) (median 0.45 vs 0.38; P=0.03). Following thrombectomy, poor outcome patients had larger 24 hour' core infarctions (median 59.5 vs 29.9 mL; P=0.01), more core infarction growth (median 33.6 vs 13.4 mL; P<0.001), and more mild (65% vs 50%; P=0.02) and severe (18% vs 0%; P=0.01) reperfusion hemorrhage. In a logistic regression analysis, the presence of any reperfusion hemorrhage (OR 3.3 [95% CI, 1.67 to 5]; P=0.001), age (OR 1.1 [95% CI, 1.03 to 1.11], P=0.004), higher NIHSS (OR 1.25 [95% CI, 1.07 to 1.41], P=0.002), and time from imaging to femoral artery puncture (OR 5 [95% CI, 1.16 to 16.67], P=0.03) independently predicted poor outcomes.

Conclusions In late time windows, both mild and severe reperfusion hemorrhage were associated with poor outcomes. Older age, higher NIHSS, and increased time from imaging to arterial puncture were also associated with poor outcomes despite successful revascularization.

Trial registration https://clinicaltrials.gov/ct2/show/NCT02586415

INTRODUCTION

Endovascular thrombectomy is an effective treatment of acute ischemic stroke (AIS) caused by large-vessel occlusion (LVO) of the internal carotid artery or proximal middle cerebral artery.[1–3] Successful revascularization increases the likelihood of achieving a good clinical outcome after treatment.[4–6] However, not all patients with successful revascularization achieve a good clinical outcome, and the reasons for poor outcome after successful thrombectomy are not well understood. Demographic and stroke severity factors, such as patient age, sex, presentation NIHSS, and initial core infarction volume influence outcome independent of thrombectomy treatment.[7–12] Modifiable factors that may be targets for therapeutic intervention to improve outcomes after successful thrombectomy are of high importance.

DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) was a late-window randomized trial that compared medical therapy with thrombectomy.[2] Patients in the thrombectomy arm of DEFUSE 3 who achieve successful revascularization (TICI 2b–3) may provide insight into factors that influence outcome despite successful thrombectomy.

We determined factors that predicted poor outcome 90 days after successful thrombectomy (TICI 2b–3) in the DEFUSE 3 trial, with an emphasis on modifiable factors that may be targets for future therapeutic interventions.

METHODS

DEFUSE 3 trial and patients

DEFUSE 3 was a multicenter, randomized trial that compared thrombectomy with medical management for the treatment of AIS due to an anterior circulation LVO in patients who were last known to be normal 6–16 hours prior to enrollment.[2] We performed a post hoc analysis of all DEFUSE 3 patients who underwent successful thrombectomy (TICI 2b–3). Informed consent was obtained for all DEFUSE 3 patients.

Imaging analysis

The DEFUSE 3 core laboratory determined imaging outcomes in a blinded manner.[2] Angiographic revascularization after thrombectomy was quantified using the modified TICI scale. Pre-thrombectomy collaterals on CT angiography (CTA) were rated with the binary modified Tan collateral scale. Tissue-level collaterals were measured on CT or MR perfusion by the hypoperfusion intensity ratio (HIR).[13 14] HIR is the volume of brain tissue with time-to-maximum (Tmax) >10 s divided by the volume of brain tissue with Tmax >6 s: volumes were quantified by RAPID (iSchemaView, Menlo Park, CA).[13 14] Cerebral hemorrhage following thrombectomy was scored on 24 hours' MRI or CT according to the European Cooperative Acute Stroke Study (ECASS) I criterium.[15]

Reperfusion was assessed on 24 hours' MR or CT perfusion studies and automatically quantified using RAPID. Hyper-perfusion within the affected

hemisphere was scored on MR or CT perfusion studies at 24 hours. Cerebral blood flow (CBF) and Tmax maps were visually scored relative to the contralateral normal hemisphere as: 0=no hyperintensity; 1=possible hyperintensity; or 2=definite hyperintensity. MR or CT perfusion studies with large cerebral hemorrhages or technical failures were excluded from the analysis. Statistical analysis was performed by dichotomizing these data into scores of 0 vs 1 or 2.

Clinical definitions and outcomes

Clinical outcomes were assessed 90 days after treatment using dichotomized modified Rankin Scale (mRS; favorable, mRS 0–2; unfavorable, mRS 3–6) at 90 days. Symptomatic intracranial hemorrhage (SICH) was defined as parenchymal or subarachnoid hemorrhage with a decline in NIHSS of ≥4 points.

Statistical analysis

Patient demographics, clinical variables, and neuroimaging data were compared between these two groups using the χ^2 and Wilcoxon rank-sum tests.

Clinical and imaging variable association with neurologic outcome was assessed using a logistic regression model that was fitted to the primary outcome and ordinal logistic regression models for secondary outcomes. The model was adjusted for age, presentation NIHSS, serum glucose at enrollment, and time from last known normal to randomization.

Analysis for trends in binomial proportions across levels of an independent factor was performed using the Cochran–Armitage test with reperfusion hemorrhage considered as an explanatory variable with ordered levels (HI1, HI2, PH1, and PH2) and mRS ≤2 as the dependent outcome.

For the ordinal logistic regression models, the proportional-odds assumption had to be met (P>0.05) before further analysis.

Alpha was set at the 0.05 level, and all reported results are two-sided. Statistical analysis was done using SAS 9.4.

RESULTS

70 patients in the endovascular arm of DEFUSE 3 achieved TICI 2b–3 and were dichotomized into good outcome (mRS 0–2; 51%) and poor outcome (mRS 3–6; 49%) groups (table 1). One of the included patients had TICI 3 on the baseline digital subtraction angiogram and this patient had been excluded from the analysis in the primary paper.[2] Poor outcome patients were older (median age 73.5 [IQR, 66–84] vs 66.5 [IQR, 57.5–75]; P=0.01), more likely female (68% vs 39%; P=0.02), and presented with a higher baseline NIHSS (20 [IQR, 15–21] vs 13 [IQR, 9–16.5]; P<0.001). CTA collaterals were similar between these two groups (P=0.72), but patients with a poor outcome had poorer perfusion collaterals (median HIR 0.45 [IQR, 0.36–0.58] vs HIR 0.38 [IQR, 0.19–0.45], P=0.03). No other differences were identified (table 1).

Table 2 shows thrombectomy treatment details. Poor outcome patients had longer groin puncture to reperfusion times (42 min [IQR, 36–69] vs 31 [IQR, 23–45] min; P=0.001). Fewer poor outcome patients achieved perfect revascularization (TICI 3; 18% vs 33%; P=0.13), but this difference was not significant.

After thrombectomy, median NIHSS at 24 hours was higher in poor outcome patients (15 [IQR, 9–22] vs 5 [IQR, 1.5–7.5];

Table 1 Patient characteristics and stroke presentation details of patients with TICI 2b–3 revascularization dichotomized by clinical outcome

	Good outcome (n=36)	Poor outcome (n=34)	P-value
Median age (years), (IQR)	66.5 (57.5–75)	73.5 (66–84)	0.01
Female sex, n (%)	14 (39)	23 (68)	0.02
Ethnicity hispanic, n (%)	8 (22)	4 (12)	0.35
Race white, n (%)	31 (86)	30 (88)	1.0
Hypertension, n (%)	26 (72)	26 (76)	0.68
Hyperlipidemia, n (%)	22 (61)	18 (53)	0.49
Atrial fibrillation, n (%)	13 (36)	14 (41)	0.66
Diabetes mellitus, n (%)	8 (22)	11 (32)	0.34
Prior stroke, n (%)	3 (8)	9 (26)	0.06
Median presentation NIHSS (IQR)	13 (9–16.5)	20 (15–21)	<0.001
Wake up stroke, n (%)			
among all	20/36 (56)	17/34 (50)	0.79
among unknown onset time (wakeup and unwitnessed)	20/22 (91)	17/25 (68)	0.08
Median time from symptom onset to inclusion, hrs:min (IQR)	11:22 (8:57–12:21)	10:53 (8:30–13:02)	0.89
Treated with IV tPA, n (%)	4 (11)	5 (15)	0.73
Occlusion site internal carotid artery, n (%)	9 (25)	14 (41)	0.15
Good collaterals on qualifying CTA, n/total (%)	18/26 (69)	17/23 (74)	0.72
Median hypoperfusion intensity ratio (HIR), (IQR)	0.38 (0.19–0.45)	0.45 (0.24–0.62)	0.03
Median ischemic core (IQR), mL	14.4 (1.0–25.6)	10.7 (6.1–38.2)	0.31
Median perfusion lesion (IQR), mL	108 (77–133)	124 (86–177)	0.11
Median time from stroke onset to qualifying imaging (IQR), hours	10:56 (8:29–11:45)	10:15 (7:55–12:07)	0.72
Median ASPECTS (IQR)	8.5 (7–9)	8 (7–9)	0.05
Right hemisphere stroke, n (%)	19 (53)	15 (44)	0.47

Table 2 Thrombectomy treatment details

	Good outcome (n=36)	Poor outcome (n=34)	P-value
General anesthesia, n (%)	6 (17)	12 (35)	0.08
Median time from stroke onset to groin puncture (IQR), hours	11:40 (9:27–12:53)	11:19 (8:46–13:20)	0.93
Median time from baseline imaging to groin puncture (IQR), min	48 (36–72)	72 (44–92)	0.07
Median time of thrombectomy procedure (IQR), min (groin puncture to reperfusion)	31 (23–45)	42 (36–69)	0.001
Median time from stroke onset to reperfusion (IQR), hours	12:16 (9:48–13:22)	12:15 (9:38–14:35)	0.66
Front-line aspiration thrombectomy, n (%)	7 (21%)	10 (29%)	0.401
Front-line stent retriever thrombectomy, n (%)	27 (79%)	24 (71%)	
Rescue after front-line aspiration by a stent retriever, n (%)	1 (14%)	3 (30%)	0.603
Rescue after front-line stent retriever by aspiration, n (%)	1 (4)	2 (8)	0.596
Mean number thrombectomy passes (SD)	1.8 (1.0)	2.1 (1.3)	0.26
Number single pass, n (%)	16 (46)	16 (47)	0.91
Final TICI score, n (%)			0.13
2b	24 (67)	28 (82)	
3	12 (33)	6 (18)	

P<0.001) (table 3). Poor outcome patients had a higher median infarct volume (59.5 [IQR, 27.2–146.9] vs 29.9 mL [IQR, 8.1–56.7]; P=0.01) and more infarct growth (33.6 [IQR, 14.5–108.2] vs 13.4 mL [IQR, 2.6–34.7]; P<0.001). There was no difference in the frequency of new strokes or in 24 hours' hyperperfusion on CBF or Tmax following thrombectomy between these groups (table 3).

Patients with reperfusion hemorrhage of any grade (61%) were more likely to have a poor outcome compared with those without any reperfusion hemorrhage (25%; P=0.004; table 3). A proportions trend analysis determined that the likelihood of a poor outcome increased with reperfusion hemorrhage severity (P<0.001; figure 1).

Logistic regression analysis identified factors predictive of a poor outcome at 90 days. Time from imaging to femoral artery puncture (OR 5 [95% CI, 1.16 to 16.67], P=0.03), any reperfusion hemorrhage (OR 3.3 [95% CI, 1.67 to 5]; P=0.001), age (OR 1.1 [95% CI, 1.03 to 1.11], P=0.004), and baseline NIHSS (OR 1.25 [95% CI, 1.07 to 1.41], P=0.002), independently predicted poor outcomes at 90 days. To determine if baseline core infarction influenced the association of reperfusion hemorrhage with poor outcomes, we adjusted for baseline core infarction (OR 1.0 [95% CI, 0.96 to 1.04], P=0.873). After adjustment, any reperfusion hemorrhage (OR 8.4 [95% CI, 1.79 to 39.49]; P=0.007), time from imaging to femoral artery puncture (OR 4.6 [95% CI, 1.24 to 16.99], P=0.023), baseline NIHSS (OR 1.23 [95% CI, 1.08 to 1.41], P=0.002), and age (OR 1.07 [95% CI, 1.01 to 1.13], P=0.021) independently predicted poor outcomes at 90 days.

Table 3 Imaging outcomes at 24 hours and clinical outcomes at 24 hours', discharge and 90 days

	Good outcome (n=36)	Poor outcome (n=34)	P-value
Median infarct volume at 24 hours (IQR)	29.9 (8.1–56.7)	59.5 (27.2–146.9)	0.01
Median Tmax6 at 24 hours (IQR)	0 (0–0)	0 (0–4.1)	0.63
Median infarct growth (IQR), mL	13.4 (2.6–34.7)	33.6 (14.5–108.2)	<0.001
Hyper-perfusion at 24 hours			
Increased CBF, n (%)	6 (21)	8 (35)	0.35
Decreased Tmax, n (%)	10 (34)	7 (33)	1.00
Reperfusion hemorrhage			0.02
HI1, n (%)	8 (22)	7 (21)	
HI2, n (%)	8 (22)	12 (35)	
PH1, n (%)	1 (3)	3 (9)	
PH2, n (%)	1 (3)	6 (18)	
Symptomatic Intracranial hemorrhage, n (%)	0 (0)	6 (18)	0.01
Recurrent stroke after thrombectomy, n (%)	2 (6)	1 (3)	1.0
Median 24 hours NIHSS (IQR)	5 (1.5–7.5)	15 (9–22)	<0.001
Median discharge NIHSS (IQR)	2.5 (1–4)	10 (5–15)	<0.001
Median mRS at 90 days (IQR)	1 (1–2)	4 (3–5)	<0.001
Mortality, n (%)	0 (0)	8 (24)	0.002

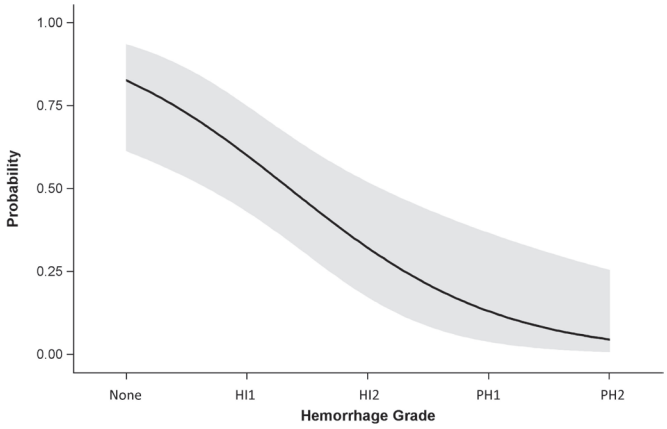

Figure 1 Likelihood of a good clinical outcome as a function of reperfusion hemorrhage. The probability of a good clinical outcome at 90 days (MRS 0–2) is plotted on the vertical axis, and the severity of reperfusion hemorrhage (HI1, HI2, Ph1, and PH2) are plotted on the horizontal axis. The shaded region reflects the 95% CI boundaries: the model is adjusted for patient age, NIHSS at the time of randomization, and the time from imaging to femoral artery puncture.

DISCUSSION

In this study, we identified factors associated with a poor clinical outcome (mRS >2) at 90 days in DEFUSE 3 patients who underwent successful thrombectomy with TICI 2b–3 revascularization. Modifiable predictors of poor outcome were the presence of any reperfusion hemorrhage and increased imaging to arterial puncture time. The severity of reperfusion hemorrhage was significantly associated with poor clinical outcomes. Patient demographic and presentation predictors of poor outcome included older age, female sex, higher NIHSS score, and larger core infarctions. Modern thrombectomy techniques result in TICI 2b–3 revascularization in 58%–88% of patients,[1–3] but up to 45% of patients had a poor outcome despite successful revascularization.[16] The findings of our study provide insights into factors that mitigate favorable outcomes despite successful thrombectomy.

Similar to our results, patient age, sex, NIHSS, core infarction volume, and thrombectomy procedure time influence outcome independent of thrombectomy success in prior studies.[7–12] Other studies have found that the likelihood of achieving functional independence after treatment is highest among patients who achieve TICI 3 revascularization.[4–6] In our study, there was a trend toward TICI 3 revascularization in patients with a good outcome (33% vs 18% in poor outcome patients), but this difference did not reach statistical significance. We hypothesize that this analysis is underpowered to determine the effect of TICI 3 revascularization on outcome.

Robust collaterals have been correlated with good clinical outcomes and lower rates of hemorrhagic transformation after thrombectomy in early time windows.[17 18] In this study, there were no differences in collateral robustness as measured by CTA between patients with good and poor outcomes following thrombectomy, which is similar to the DEFUSE 3 prespecified collateral analysis.[19] CTA collaterals in DEFUSE 3 were largely determined by single-phase CTA, which may limit collateral assessment compared with multiphase collaterals and partially explain our results. By contrast, patients with a good outcome were more likely to have a favorable HIR collateral profile on baseline CT or MR perfusion imaging. This result suggests that robust tissue-level collateral blood flow is a favorable prognostic maker, which is similar to other studies that have found a favorable HIR (<0.4) to be a marker of thrombectomy eligibility, penumbra preservation, and slow core infarct growth.[13 14 20]

Prior studies have suggested that increased cerebral perfusion on arterial spin labeling MRI[21 22] following thrombectomy is a predictor of poor clinical outcomes.[21 22] We did not find an association between hyper-perfusion and clinical outcome in our study, which might be due to the use of different imaging modalities.

Interestingly, the presence of any reperfusion hemorrhage was significantly associated with worse 90-day outcomes after successful thrombectomy. SICH caused by large reperfusion parenchymal hematomas (PH2) or subarachnoid hemorrhage following thrombectomy occurs in 5%–7% of patients[1–3] and is a known predictor of poor outcome.[23] By contrast, less severe reperfusion hemorrhage that includes petechial hemorrhage (HI1 and HI2) and smaller parenchymal hematomas (PH1) are thought to be largely asymptomatic[15 23] and occurs in 30%–43% of thrombectomy patients.[24 25]

The importance of mild reperfusion hemorrhage following stroke treatment remains uncertain. Some have considered mild reperfusion hemorrhage to be a marker of successful reperfusion and favorable outcome after intravenous thrombolysis,[26] whereas other studies found mild reperfusion hemorrhage to be correlated with poor outcomes.[12 27 28] Mild reperfusion hemorrhage after thrombectomy in early time windows has been associated with worse 90-day outcomes (mRS 3–6)[25] or a reduced risk of an excellent outcome (mRS 0–1),[29] which is similar to our findings after late time window thrombectomy.

The mechanism by which reperfusion hemorrhage hinders clinical outcome remains unknown. Blood-brain barrier breakdown, oxidative brain injury, hemolysis, hemorrhage resorption, and cerebral inflammation are all possible mechanisms by which reperfusion hemorrhage may promote or exacerbate brain injury,[30] but additional study is needed to understand better the pathophysiology of reperfusion hemorrhage brain injury.

Our study has important implications for future studies of neuroprotection in AIS. Our findings suggest that neuroprotective agents or maneuvers that lead to blood-brain barrier stabilization and reduced reperfusion hemorrhage immediately prior to, at the time of, or immediately following thrombectomy should be considered as priority studies in neuroprotection. Future studies should explore whether neuroprotective agents, careful blood pressure modulation after thrombectomy, and administration of antiplatelet or anticoagulation medications affect reperfusion hemorrhage and patient outcomes.

Lastly, our finding that reduced time from imaging to arterial puncture is associated with improved outcomes after thrombectomy requires additional study in a larger cohort of patients. The reasons for the difference in time from imaging to arterial puncture between these two groups is not entirely clear, and it is possible that the non-significant increase in general anesthesia use in patients with a poor outcome may partially account for these differences. Our finding suggests that efforts to ensure that thrombectomy workflows are highly streamlined to minimize time delays are important and may improve patient outcomes.

Our study is limited by the relatively small sample of this cohort and the post-hoc design.

CONCLUSIONS

In DEFUSE 3 late time window patients, mild and severe reperfusion hemorrhage were associated with poor outcomes following successful thrombectomy (TICI 2b–3). Increased imaging to arterial puncture time, older age, female sex, and higher NIHSS

were also associated with poor outcomes. These findings raise the possibility that adjunctive therapies that prevent reperfusion hemorrhage might improve outcomes from thrombectomy.

Twitter Jeremy J Heit @JeremyHeitMDPHD

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Competing interests JJH: Medtronic (consulting); MicroVention (consulting), iSchemaView, Inc (Medical and Scientific Advisory Board) SC: iSchemaView, Inc (equity and consulting) MGL: Novo Nordisk, Genentech/Roche, Biogen and Moleac. Principal investigator on NIH and Neofect research grants. MPM: ThrombX Medical, Inc (ownership interest). AWG: iSchemaView, Inc (equity and consulting); Medtronic (consulting).

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ORCID iDs
Jeremy J Heit http://orcid.org/0000-0003-1055-8000
Jean-Marc Olivot http://orcid.org/0000-0003-2027-2276

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