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ORIGINAL RESEARCH

Predictors of poor outcome despite recanalization: a multiple regression analysis of the NASA registry

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ABSTRACT

Background Mechanical thrombectomy with stent-retrievers results in higher recanalization rates compared with previous devices. Despite successful recanalization rates (Thrombolysis in Cerebral Infarction (TICI) score ≥2b) of 70–83%, good outcomes by 90-day modified Rankin Scale (mRS) score ≤2 are achieved in only 40–55% of patients. We evaluated predictors of poor outcomes (mRS >2) despite successful recanalization (TICI ≥2b) in the North American Solitaire Stent Retriever Acute Stroke (NASA) registry.

Methods Logistic regression was used to evaluate baseline characteristics and recanalization outcomes for association with 90-day mRS score of 0–2 (good outcome) vs 3–6 (poor outcome). Univariate tests were carried out for all factors. A multivariable model was developed based on backwards selection from the factors with at least marginal significance ($p \leq 0.10$) on univariate analysis with the retention criterion set at $p \leq 0.05$. The model was refit to minimize the number of cases excluded because of missing covariate values; the c-statistic was a measure of predictive power.

Results Of 354 patients, 256 (72.3%) were recanalized successfully. Based on 234 recanalized patients evaluated for 90-day mRS score, 116 (49.6%) had poor outcomes. Univariate analysis identified an increased risk of poor outcome for age ≥80 years, occlusion site of internal carotid artery (ICA)/basilar artery, National Institute of Health Stroke Scale (NIHSS) score ≥18, history of diabetes mellitus, TICI 2b, use of rescue therapy, not using a balloon-guided catheter or intravenous tissue plasminogen activator (IV t-PA), and >30 min to recanalization ($p \leq 0.05$). In multivariable analysis, age ≥80 years, occlusion site ICA/basilar, initial NIHSS score ≥18, diabetes, absence of IV t-PA, ≥3 passes, and use of rescue therapy were significant independent predictors of poor 90-day outcome in a model with good predictive power (c-index=0.80).

Conclusions Age, occlusion site, high NIHSS, diabetes, no IV t-PA, ≥3 passes, and use of rescue therapy are associated with poor 90-day outcome despite successful recanalization.

INTRODUCTION

Recanalization of the occluded artery is a powerful predictor of good outcome in acute ischemic stroke secondary to large artery occlusion.[1–4] Mechanical thrombectomy with stent-retrievers results in higher recanalization rates and better outcomes than previous devices such as the Concentric Thrombus Retriever. However, despite rates of successful recanalization (Thrombolysis in Cerebral Infarction (TICI) score ≥2b) up to 85%, good clinical outcomes assessed by modified Rankin Scale (mRS) ≤2 are achieved in only up to 55% of patients.[2–7]

Some authors have identified factors that influence poor outcomes in patients with acute stroke treated with the Merci thrombectomy device. In particular, the multi MERCI trial identified absence of successful recanalization, age, high National Institute of Health Stroke Scale (NIHSS) score, and proximal vessel occlusion as predictors of mortality.[1 8] However, it is not clear which factors increase the risk of a poor clinical outcome despite recanalization.

The North American Solitaire Acute Stroke (NASA) registry is a multicenter, non-sponsored, physician-conducted, post-marketing registry on the use of the Solitaire FR device in 354 patients with acute large vessel ischemic stroke. Recanalization rates and clinical outcomes reported in NASA[7] were comparable to the data from the randomized trials SWIFT[5] and TREVO.[6]

The present study evaluated baseline characteristics and recanalization parameters for association with poor outcomes (mRS ≥3) in successfully recanalized (TICI ≥2b) cases from the NASA registry of patients with acute stroke treated with the Solitaire FR device.

METHODS

Research participants

Study participants (de-identified data) were obtained from the NASA registry of patients treated with the Solitaire FR as the only device for restoration of blood flow. The NASA registry recruited

24 clinical sites within North America to submit retrospective demographic, clinical presentation, site-adjudicated angiographic, procedural, and clinical outcome data on consecutive patients with acute stroke treated within 8 h of symptom onset with the Solitaire FR device from March 2012 to February 2013. Details of the NASA participant population can be found in the original report.[7]

Data

In addition to patient demographics, registry data included information on revascularization and clinical outcomes. Thrombolysis in Myocardial Infarction (TIMI) and TICI scores were determined based on the final angiogram after the procedure was completed. Successful recanalization was defined as TICI ≥2b. Clinical outcomes included whether or not patients developed a symptomatic intracranial hemorrhage upon 24 h CT follow-up; mRS score at discharge, 30 and 90 days post-treatment; NIHSS score at pretreatment, discharge, and 90 days post-treatment; and mortality. A good clinical outcome was defined as mRS ≤2 at 90 days.

Statistical analysis

Descriptive statistics were used to characterize study patients at baseline and recanalization outcomes. Counts and percentages are reported for categorical variables; continuous variables are summarized as mean (SD) or median (range). Baseline characteristics included demographics, comorbidities, site of stroke, and initial NIHSS score. Recanalization outcomes included post-procedure TICI score, number of passes, use of intravenous tissue plasminogen activator (IV t-PA), balloon-guided catheter (BGC), Penumbra or rescue therapy, time from symptom onset to treatment start, and time from treatment start to recanalization.

Logistic regression was used to evaluate baseline characteristics and recanalization results for association with 90-day outcomes characterized as good (mRS 0–2) or poor (mRS 3–6). First, univariate tests were carried out for all factors except time from onset to treatment initiation (see below). Age and time to recanalization were modeled categorically after determining that the linearity assumption (constant risk per unit change) did not hold. Category cut-off points for these variables were then derived from data quartiles. Quartile analysis was also used for initial testing of NIHSS.

Next, a multivariable model was developed based on backwards selection from the set of factors with at least marginal significance ($p \le 0.10$) on univariate analysis. The retention criterion was set at $p \le 0.05$. The resulting model was refit to minimize the number of cases excluded because of missing covariate values, and the c-statistic was used as a measure of predictive power. The sensitivity of model results to missing outcome data was also evaluated. This analysis was done using the most recent available mRS score (last observation carried forward (LOCF) method) and also under the worst case assumption of poor outcome for all cases with missing 90-day mRS scores.

Time from onset to treatment initiation was evaluated in a separate analysis restricted to the subset of anterior site cases treated within 8 h of symptom onset. The restriction was necessary because posterior site cases tended to have less urgent symptoms and greater tolerance of delayed treatment.

Statistical analysis was carried out using SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The NASA registry enrolled 354 consecutive patients with acute ischemic stroke treated with the Solitaire FR device.[7] Of these, 256 (72.3%) were successfully recanalized (TICI 2b–3) and 234 recanalized patients had 90-day mRS scores as required entry criteria for our analysis. Baseline characteristics and recanalization outcomes for study patients are summarized in table 1.

At 90-day follow-up, 118 (50.4%) patients were classified as having a good outcome (mRS 0–2) while 116 (49.6%) had a poor outcome (mRS 3–6). An analysis of factors associated with a poor outcome following recanalization is presented in table 2. Univariate tests identified an increased risk for each of the following: age ≥80 years (upper quartile of data), internal carotid artery (ICA)/basilar site, median initial NIHSS score ≥18, diabetes mellitus (DM), final TICI 2b, BGC not used, IV t-PA not used, time to recanalization (≥30 min vs <30 min), and use of rescue therapy ($p<0.05$). No association was found for sex, race, smoking, atrial fibrillation, coronary artery disease, hypertension,

Table 1 Baseline characteristics and recanalization outcomes for 234 patients

Baseline characteristics	Mean N	SD %
Mean age, years	66.9	14.7
Sex (1)		
Female	119	51.1
Male	114	48.9
Race (1)		
White	179	76.8
Black	39	16.7
Other	15	6.4
Smoking (3)	67	29.0
Atrial fibrillation	98	41.9
Diabetes mellitus	61	26.1
Hypertension	174	74.4
Hyperlipidemia	124	53.0
Coronary artery disease	76	32.5
Location of clot/occlusion		
M1	136	58.1
M2	23	9.8
ICA	48	20.5
Basilar	27	11.5
NIHSS, baseline (6)		
Mild: 0–5	10	4.4
Moderate: 6–19	127	55.7
Severe: 20–42	91	39.9
Recanalization outcomes		
Final TICI score		
2b	107	45.7
3	127	54.3
Rescue therapy, Solitaire failed	48	20.5
Distal embolization (2)	36	15.5
Balloon-guided catheter (10)	98	43.8
Solitaire+Penumbra (10)	32	14.3
Intravenous t-PA (1)	100	42.9
Intra-arterial t-PA	65	27.8
Passes (1)		
1–2	198	84.9
≥3	35	15.0
Median (range) time from onset to procedure start (8), min	277	75–1425
Median (range) time from procedure start to recanalization (25), min	45	8–412

Data shown are n (%) unless indicated otherwise.
ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; t-PA, tissue plasminogen activator.

Table 2 Effect of baseline characteristics and recanalization outcomes on risk of poor 90-day outcome (mRS 3–6)

	N (%) with risk factor							
	Good (mRS 0–2)	Poor (mRS 3–6)	Crude OR	95% CI	p Value	Adjusted OR	95% CI	p Value
Baseline characteristics								
Age ≥80 vs <80 years	20/118 (17)	33/116 (28)	1.95	(1.04 to 3.65)	0.037	2.50	(1.21 to 5.19)	0.014
Male vs female	52/117 (44)	62/116 (53)	1.44	(0.86 to 2.40)	0.170	–	–	–
Black vs white	19/117 (16)	20/116 (17)	1.09	(0.54 to 2.18)	0.810	–	–	–
Other race vs white	7/117 (6)	8/116 (7)	1.18	(0.41 to 3.40)	0.757	–	–	–
Smoking	39/117 (33)	28/114 (25)	0.65	(0.37 to 1.16)	0.143	–	–	–
Atrial fibrillation	46/118 (39)	52/116 (45)	1.27	(0.76 to 2.14)	0.366	–	–	–
Diabetes mellitus	22/118 (19)	39/116 (34)	2.21	(1.21 to 4.04)	0.010	2.82	(1.37 to 5.83)	0.005
Hypertension	85/118 (72)	89/116 (77)	1.28	(0.71 to 2.31)	0.412	–	–	–
Hyperlipidemia	61/118 (52)	63/116 (54)	1.11	(0.66 to 1.86)	0.689	–	–	–
Coronary artery disease	34/118 (29)	42/116 (36)	1.40	(0.81 to 2.43)	0.228	–	–	–
ICA/basilar site vs M1/M2	29/118 (25)	46/116 (40)	2.02	(1.15 to 3.53)	0.014	2.18	(1.10 to 4.33)	0.026
NIHSS ≥18 vs ≤17	42/117 (36)	73/111 (66)	3.43	(1.99 to 5.91)	<0.001	4.51	(2.33 to 8.71)	<0.001
Recanalization outcomes								
Final TICI 2b vs 3	46/118 (39)	61/116 (53)	1.74	(1.03 to 2.92)	0.037	–	–	–
Rescue therapy, Solitaire failed	12/118 (10)	36/116 (31)	3.97	(1.94 to 8.12)	<0.001	4.94	(2.14 to 11.43)	<0.001
Distal embolization	20/116 (17)	16/116 (14)	0.77	(0.38 to 1.57)	0.469	–	–	–
Balloon-guided catheter not used	54/113 (48)	72/111 (65)	2.02	(1.18 to 3.45)	0.010	–	–	–
Solitaire+Penumbra	14/113 (12)	18/111 (16)	1.37	(0.64 to 2.91)	0.414	–	–	–
Intra-arterial t-PA not used	89/118 (75)	80/116 (69)	0.72	(0.41 to 1.29)	0.271	–	–	–
Intravenous t-PA not used	57/118 (48)	76/115 (66)	2.09	(1.23 to 3.54)	0.006	2.81	(1.47 to 5.36)	0.002
Passes ≥3 vs 1–2	13/117 (11)	22/116 (19)	1.87	(0.89 to 3.93)	0.097	2.62	(1.03 to 6.69)	0.043
Time to recanalization ≥30 min vs <30 min	69/105 (66)	86/104 (83)	2.49	(1.28 to 4.59)	0.006	–	–	–

p Value: Wald statistic. ORs estimate the risk of a poor 90-day outcome for patients with versus without the factor shown at left except where other categories are indicated. Crude ORs were estimated from univariate logistic regression; adjusted ORs from a multivariable model with the covariates shown (226 cases).
ICA, internal carotid artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction; t-PA, tissue plasminogen activator.

hyperlipidemia, distal embolization, use of Solitaire in association with the Penumbra, and intra-arterial (IA) t-PA.

In multivariable analysis, age ≥80 years, ICA/basilar site, initial NIHSS score ≥18, DM, absence of IV t-PA, ≥3 passes, and use of rescue therapy were significant independent predictors of poor 90-day outcome. The model, which used 226 cases, had a c-index of 0.80 (95% CI 0.74 to 0.86), indicating good predictive power.

Data were insufficient to consider the prognostic effect of blood pressure, embolization to new territory (only 4 cases), transfer and transfer type (45 missing values), general anesthesia (45 missing values), fluoroscopy time (36 missing values), or time from door to groin puncture (76 missing values). Development of symptomatic intracranial hemorrhage was not included in the regression analysis because it is not known until 24 h after procedure completion.

Sensitivity analysis with respect to missing 90-day mRS scores for 22 recanalized patients confirmed the prognostic effects shown in table 2, with some differences in statistical significance as follows. Under LOCF and worst case assumptions, site was at most marginally significant (OR 1.7, $p=0.110$ and OR 1.8, $p=0.068$, respectively). LOCF but not worst case assumptions also resulted in the loss of significance for number of passes (OR 1.7, $p=0.195$). These models included 246 and 247 cases, respectively.

Subset analysis of anterior cases (M1, M2, ICA) with respect to total time to recanalization was based on 154 cases for which treatment was started within 8 h of symptom onset. Total time was marginally significant ($p=0.055$), with an estimated 9% increased risk of poor outcome per 30 min increase in time from onset to recanalization.

DISCUSSION

A large body of literature shows that, in acute ischemic stroke, recanalization is a powerful predictor of good outcomes. Notably, a meta-analysis by Rha and Saver[9] of 53 articles published between 1985 and 2002 reported data on 1774 patients evaluated for vessel recanalization. Based on 33 of the studies totaling 998 patients, their meta-analysis reported that good outcomes were more frequent in the recanalized group at 3 months (OR 4.43;95% CI 3.32 to 5.91) and 3-month mortality was reduced (OR 0.24; 95% CI 0.16 to 0.35).[9] Interestingly, mechanical thrombectomy in SWIFT, STAR and NASA yielded similar results—namely, a significant increase in the odds of a good outcome (OR 4.87; 95% CI 2.59 to 9.14) and a risk reduction of approximately 60% for mortality (OR 0.38; 95% CI 0.23 to 0.65). Thus, the benefit of recanalization is well established. It remains important to understand which factors influence poor outcomes despite adequate recanalization.

In our study of patients with acute stroke in the NASA registry with recanalization of the occluded artery, several factors emerged as predictors of poor outcomes (mRS ≥3). In particular, age ≥80 years, occlusion site other than M1/M2, NIHSS score ≥18, DM, absence of pretreatment with IV t-PA, ≥3 passes with the Solitaire device, and use of rescue therapy were identified as significant independent predictors of poor 90-day outcome. The strongest effects were NIHSS score and rescue therapy, both of which increased the risk of a poor outcome approximately fourfold whereas the increase estimated for each of the other factors was 2–3.

Age (>80 years) has previously been associated with poor outcome in patients treated with IV t-PA[8] and intra-arterial therapy (IAT) in an analysis of the PROACT II data.[10 11] It has been hypothesized that age per se significantly impacts clinical outcomes after cerebral ischemia regardless of the presence of reperfusion. Very recently, Ribo *et al*[12] analyzed the relationship between outcomes and final infarct volume (FIV) in 214 patients stratified by age. Similar to the data reported by Yoo *et al*,[13] Ribo *et al* also reported that a FIV of ≤49 mL predicts a mRS score of ≤2 in patients aged <70 years. Interestingly, the authors found that the FIV threshold for good outcomes decreased to 32.5 mL in patients aged 70–79 years and to 15.2 mL in patients aged ≥80 years. The oldest age group had the smallest proportion of patients at or below the age-adjusted FIV threshold (14–44% depending on the initial Alberta Stroke Program CT Score (ASPECTS) vs 29–65% in the two younger age strata). The data have to be considered in light of the fact that ischemic stroke in elderly patients without recanalization either by thrombectomy or after IV t-PA is associated with very high rates of death and severe disability.[14 15] In particular, patients aged >80 years with acute ischemic stroke have higher risk-adjusted fatality, longer hospitalization, and are less likely to be discharged home than younger patients.[15] These consistent findings may be explained by the very low tolerance of elderly brain to volumes of infarction that are otherwise tolerated in younger patients and the decreased plasticity of neuronal networks as age advances. Nevertheless, elderly patients should be considered for acute endovascular intervention because of their extremely poor outcomes without any treatment. However, one has to consider that, even after successful recanalization, their outcomes may not be comparable to younger patients.

A high NIHSS score on admission has previously been correlated with poor outcomes after IV and IAT by several studies.[16–18] In our analysis of the NASA data the NIHSS score was predictive of poor outcomes despite recanalization, in line with previous reports.[16–18] The results seem to indicate that the task of reversing a high neurological deficit at presentation is difficult to accomplish. These data also show the dilemma of considering patients with high NIHSS for IAT and their inclusion in clinical trials. In this regard, the SYNTHESIS trial concluded that endovascular treatment was not superior to IV t-PA in patients with acute stroke presenting with a median NIHSS score of 13.[19] However, in the SYNTHESIS trial, mechanical thrombectomy was used only in 33.3% of patients and more than 30% of patients with acute stroke presented with a NIHSS score ≤10.[19] Interestingly, in IMS III, patients with a NIHSS score >20 had better outcomes with IAT than patients treated with IV t-PA alone.[20] This finding suggests that patients who present with severe neurological deficits (as indicated by a high NIHSS score) have even poorer outcomes with IV therapy or medical management than with thrombectomy.

Acute ICA or basilar artery occlusion are known to be associated with poor outcomes.[21] In particular, distal ICA occlusion and/or tandem occlusions (ICA plus middle cerebral artery (MCA)) carry a worse prognosis than MCA occlusions.[22] In addition, it has been reported that ICA occlusions have a poorer response to IV t-PA than MCA occlusions.[23 24] In another series, Zaidat *et al*[25] examined patients with acute occlusion of the distal ICA treated with IAT/IV rt-PA. In their study the mortality rate was 50% despite complete recanalization (80% in the combined IV/IA thrombolysis group and 62% in the group treated with IAT alone). In particular, patients with ICA, MCA, and anterior cerebral artery (terminus T) occlusions were the least likely to respond to thrombolysis and only 38.9% of the patients showed moderate-to-good outcomes (90-day mRS ≤3). As a result, patients with proximal ICA occlusions or basilar occlusions are excluded from most of the clinical trials on acute stroke intervention. The correlation may be the result of a high initial infarct volume with proximal arterial occlusion. It is conceivable that, in proximal arterial occlusion, there may be technical difficulties in recanalizing the occluded vessel which results in a longer time to achieve recanalization. In this study there was an increased median time to recanalization for sites other than M1/M2 (51 min vs 44 min); however, the difference was not statistically significant (p=0.260, Wilcoxon test).

The need for ≥3 passes of the Solitaire FR and the use of rescue therapy were both retained in our multivariable model, whereas longer time to achieve successful recanalization was eliminated despite its significance on univariate analysis. This is explained by the fact that both the number of passes and rescue therapy were associated with longer recanalization times. Median time to recanalization for cases that required ≥3 passes was 85 min compared with 41 min when 1–2 passes were sufficient. Similarly, median time to recanalization was 78 min versus 41 min depending on whether rescue therapy was needed. Both associations were significant (p<0.001, Wilcoxon test).

Dramatic time sensitivity of the cerebral tissue to ischemia in acute ischemic stroke secondary to large artery occlusion has been shown by Saver.[26] Time dependency to initiation of thrombolysis was already shown in a large meta-analysis of all IV t-PA trials[27] and by other authors.[28] The lack of benefit from acute stroke intervention in IMS III and SYNTHESIS trials may also be related to delayed time to recanalization and therefore futile reperfusion.[16 19 20] Based on the IV t-PA data, there is a global effort to shorten as much as possible the time from symptom onset to intervention and door to needle. Similar to treatment with IV t-PA, Pereira *et al*[29] have shown better outcomes in patients treated with mechanical thrombectomy early compared with later. Thus, several authors have already highlighted the importance of shortening as much as possible the time from image to groin puncture and from puncture to recanalization. The result of this analysis shows that the time dependency of intervention is critical to avoid futile reperfusion, as indicated by poor outcomes despite recanalization. The data suggest that faster time to intervention is probably associated with improved clinical outcomes.

Very recently Shi *et al*[30] reported an analysis of factors that may predict poor outcomes despite recanalization. The authors reported pooled data from the multi MERCI, TREVO, and TREVO 2 trials. Although the aim of their study was similar to ours, there are differences in their data acquisition. In particular, they analyzed pooled data obtained from patients treated with different devices (ie, Concentric Retriever and Trevo) that have been shown to be different in effectiveness for recanalization. Shi *et al* also used different recanalization scales (ie, TIMI vs TICI). Recanalization in the NASA registry was obtained with the Solitaire FR and assessed by TICI score in all 354 patients. Nevertheless, similar to our analysis, they report that advanced age, high NIHSS score, and delay from symptom onset to recanalization are predictors of dependency despite recanalization. Interestingly, the authors report an increase of 11% in the odds of functional dependence (mRS >3) for every 30 min delay from symptom onset to endovascular intervention. In our analysis of the NASA data, total time to recanalization was marginally significant (p=0.055) on univariate analysis with an estimated 9% increased risk of poor outcome (mRS >2) per 30 min delay in endovascular intervention. This difference may be because they analyzed pooled data from patients treated with the Concentric Retriever and Trevo whereas we analyzed data from patients treated with Solitaire FR.

Limitations of the study

Our analysis has several limitations. In the NASA registry, assessment of reperfusion and clinical outcomes was obtained without a core laboratory or requirement of an independent adjudicator. Nevertheless, recanalization rates and outcomes in the NASA registry are strikingly similar to controlled trials on mechanical thrombectomy with stent-retrievers (ie, SWIFT and TREVO trials).[5–7] It has been reported that ischemic core imaging,[13] ASPECT score, and collateral circulation assessment may correlate with outcomes after thrombectomy.[29 31] In the NASA registry the ASPECT score and collateral circulation assessment was not performed systematically so these variables, although of great interest, were not available on all patients and are not therefore included in the analysis. Finally, there are inherent limitations in a retrospective study based on registry data acquired according to pre-established specifications.

CONCLUSIONS

In acute ischemic stroke secondary to large artery occlusion, revascularization of the occluded artery is unquestionably a powerful predictor of good outcome. Nevertheless, with the current technology and logistics, unfavorable outcomes (mRS ≥3) occur in 49% of patients despite successful recanalization. In these patients, older age, presentation with severe neurological deficit, delays to reperfusion, diabetes, occlusion site, and not receiving IV t-PA are important factors that predict poor clinical outcomes. Reducing delays in reperfusion, considering all these factors, may be the best way to improve clinical outcomes and should be considered in clinical trials that evaluate IA thrombectomy.

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Contributors IL developed the idea for the manuscript and participated in the design, concept, and data gathering for the NASA registry. IL, AKS, and GRW participated in data analysis, writing, and meaningful editing on the manuscript. GD, ACC, RG, C-HJS, CM, WEH, NM-K, JDE, TWM, FAM, HB, AX, ATR, MTF, AB, TNN, MAT, MGA, VJ, HS, RN, AJY, AA-C, PRC, GWB, RK, AN, MAI, RGN, and OOZ participated in the design, conception, and data gathering for the NASA registry, meaningful editing of the manuscript, and provided suggestions and feedback on the manuscript. All authors approved the final manuscript.

Competing interests None.

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