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# Toward a more inclusive paradigm: thrombectomy for stroke patients with pre-existing disabilities

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## ABSTRACT

**Background** Persons with pre-existing disabilities represent over one-third of acute stroke presentations, but account for a far smaller proportion of those receiving endovascular thrombectomy (EVT) and thrombolysis. This is despite existing ethical, economic, legal, and social directives to maximize equity for this vulnerable population. We sought to determine associations between baseline modified Rankin Scale (mRS) and outcomes after EVT.

**Methods** Individuals who underwent EVT were identified from a prospectively maintained database. Demographics, medical history, presentations, treatments, and outcomes were recorded. Baseline disability was defined as baseline mRS≥2. Accumulated disability was defined as the delta between baseline mRS and absolute 90-day mRS.

**Results** Of 381 individuals, 49 had baseline disability (five with mRS=4, 23 mRS=3, 21 mRS=2). Those with baseline disability were older (81 vs 68 years, P<0.0001), more likely female (65% vs 49%, P=0.032), had more coronary disease (39% vs 20%, P=0.006), stroke/TIA history (35% vs 15%, P=0.002), and higher NIH Stroke Scale (19 vs 16, P=0.001). Baseline mRS was associated with absolute 90-day mRS ≤2 (OR=0.509, 95%CI=0.370–0.700). However, baseline mRS bore no association with accumulated disability by delta mRS ≤0 (ie, return to baseline, OR=1.247, 95%CI=0.943–1.648), delta mRS ≤1 (OR=1.149, 95%CI=0.906–1.458), delta mRS ≤2 (OR 1.097, 95% CI 0.869–1.386), TICI 2b–3 reperfusion (OR=0.914, 95%CI=0.712–1.173), final infarct size (P=0.853, β=−0.014), or intracerebral hemorrhage (OR=0.521, 95%CI=0.244–1.112).

**Conclusions** While baseline mRS was associated with absolute 90-day disability, there was no association with accumulated disability or other outcomes. Patients with baseline disability should not be routinely excluded from EVT based on baseline mRS alone.

## INTRODUCTION

Persons with pre-existing disabilities represent over one-third of presenting acute stroke patients, yet account for a far smaller proportion of cases receiving interventions including endovascular thrombectomy (EVT).[1 2] The reasons for these disparities are underexplored, despite unprecedented recent advances in acute stroke care and unambiguous ethical, economic, legal, and social directives to maximize equity for this vulnerable population.[3–6] While current American Stroke Association guidelines specify EVT "may be reasonable" for patients with prestroke disability,[7] institutional policies and individual decisions to withhold treatment on the basis of prestroke disability remain common.[2 8] Even if beneficial treatment effects are recognized, clinicians may speciously assume that certain treatment measures are outside the goals of care of individuals with pre-existing disability, and due to these cognitive biases misdirect persons with disability toward non-interventional, comfort-focused care.[2 9 10]

The challenge of the available evidence base is partly due to trial selection paradigms that exclude patients with disabilities, usually for modified Rankin Scale (mRS) score greater than 1 or 2. Since stroke trial outcomes are dichotomously constructed as functional independence (mRS ≤2) vs dependence (mRS ≥3), excluding persons with pre-existing disability is intended to amplify the likelihood of detecting treatment effects.[8] An unfortunate consequence is that resultant data do not represent the entire population of ischemic stroke presentations. These gaps in the available evidence risk speculative or faulty assumptions about prognosis, quality of life, and optimal therapeutic approaches in persons with disabilities who experience stroke.[2]

Here we endeavor to help fill this evidence gap by studying associations between baseline mRS and post-EVT outcomes. Shedding light on outcomes of patients with pre-existing disability enables clinicians to more knowledgeably navigate acute decision-making for this population.

## METHODS

Patients who underwent anterior circulation EVT for large-vessel occlusion stroke were identified retrospectively from a prospectively maintained database[11] at a large tertiary referral center from January 2011 to September 2019. This database includes demographic information, medical history, clinical presentation, treatments, and outcomes for consecutive EVT patients.

Baseline and absolute 90-day mRS were determined, ranging from 0 (no symptoms) to 6 (death).[12] Baseline mRS was prospectively recorded in the database by clinical/research staff formally certified in mRS assessment[13] for 83% of patients and by chart review blinded to outcome for the remainder. Baseline disability was defined as prestroke mRS≥2. 90-day mRS was obtained by telephone call by certified clinical/research staff and was available for 89% of patients. Accumulated disability was defined as the difference (delta) between baseline and absolute 90-day mRS.

Admission NIH Stroke Scale (NIHSS) scores were determined. Alteplase treatment decisions were guideline-based at the discretion of a vascular neurologist.[7] EVT treatment decisions were at the discretion of a vascular neurologist and neurointerventionalist. While decisions were made on a case-by-case basis, considerations may have included NIHSS, time from last known well, baseline mRS, life expectancy, occlusion location, ASPECTS, collateral pattern, and infarct core volume. There were no absolute contraindications for any variables, but care team discussions and goals of care considerations were common for baseline mRS ≥4. Cervical ICA disease was defined as severe stenosis (>70%) or occlusion by NASCET criteria.[14] Thrombolysis in cerebral infarction (TICI) scores were determined using the modified scale: 2b partial filling ≥50%, 3 complete perfusion.[12] Infarcts were traced from pre-EVT (available for 43%) and post-EVT (44%) MRIs by a vascular neurologist using Slicer version 4.8.1 (Brigham and Women's Hospital, Boston, MA, USA), blinded to clinical data. RegLSM (University of Calgary, Calgary, Alberta, Canada) was used to register these to MNI-152 space, and FSL (FMRIB Analysis Group, Oxford, UK) was used to calculate volumes. Intracerebral hemorrhage (ICH) was defined as PH1 or PH2 by ECASS criteria.[12]

Differences in variables comparing mRS dichotomized 0–1 vs 2–4 were assessed using nonparametric Wilcoxon rank-sum for continuous variables and Fisher's Exact tests for categorical variables. Logistic and linear regressions were performed for independent ordinal mRS with dependent categorical variables and dependent natural logarithm-transformed infarct volume, respectively. Results are shown unadjusted and adjusted for age, sex, hypertension, diabetes, atrial fibrillation, smoking, NIHSS, and pre-EVT infarct volume. Two-tailed P-values<0.05 were considered statistically significant. Analyses were performed with SPSS version 23.0 (IBM Corp, Armonk, New York, USA). This study was approved by the local institutional review board. Informed consent was waived based on minimal patient risk and practical inability to perform the study without the waiver.

## RESULTS

381 patients, 49 with baseline disability (five with mRS=4, 23 with mRS=3, 21 with mRS=2), were identified who underwent EVT. Those with baseline disability were older (81 vs 68 years, P<0.0001), more likely to be female (65% vs 49%, P=0.032), had more coronary disease history (39% vs 20%, P=0.006), more stroke/TIA history (35% vs 15%, P=0.002), and higher presenting NIHSS (19 vs 16 points, P=0.001). There were no differences in other medical history or treatments, although a non-significant difference in alteplase administration was noted (43% vs 57%, P=0.067) (table 1).

Those with baseline disability had similar TICI 2b–3 reperfusion (78% vs 78%, P=0.855), ICH (2% vs 7%, P=0.340), and final median infarct volume (68cc vs 45cc, P=0.828). With regard to 90-day outcomes, those with baseline disability were less likely to have absolute mRS ≤2 (14% vs 45%), but no differences were observed for accumulated disability by delta mRS ≤0 (ie, return to baseline, 24% vs 16%, P=0.272), delta mRS ≤1 (45% vs 34%, P=0.168), or delta mRS ≤2 (55% vs 49%, P=0.511) (table 2).

Higher baseline mRS decreased the odds of absolute 90-day mRS ≤2 (P<0.0001, OR=0.509, 95%CI=0.370–0.700). However, baseline mRS was not associated with accumulated disability by delta mRS ≤0 (ie, return to baseline, P=0.121, OR=1.247, 95%CI=0.943–1.648), delta mRS ≤1 (P=0.251, OR=1.149, 95%CI=0.906–1.458), or delta mRS ≤2 (P=0.436, OR 1.097, 95%CI 0.869 to 1.386). Furthermore, baseline mRS was not associated with TICI 2b–3 (P=0.480, OR=0.914, 95%CI=0.712–1.173), final infarct size (P=0.853, beta=−0.014), or ICH (P=0.092, OR=0.521, 95%CI=0.244–1.112). Adjusting for age, sex, vascular risk factors, NIHSS, and pre-EVT infarct volume did not significantly change these results (table 3).

**Table 1** Baseline demographics, past medical history, and clinical presentation for patients with baseline modified Rankin Scale (mRS) dichotomized 0–1 vs 2–4

| | Baseline mRS 0–1 | Baseline mRS 2–4 | P value |
|---|---|---|---|
| Age, median (IQR) | 68 (56–79) | 81 (71–88) | <0.0001 |
| Female, count (%) | 161 (49%) | 32 (65%) | 0.032 |
| Atrial fibrillation, count (%) | 118 (36%) | 18 (37%) | 0.874 |
| Diabetes, count (%) | 66 (20%) | 13 (27%) | 0.344 |
| Hypertension, count (%) | 219 (66%) | 37 (76%) | 0.197 |
| Coronary artery disease, count (%) | 67 (20%) | 19 (39%) | 0.006 |
| Stroke/TIA, count (%) | 51 (15%) | 17 (35%) | 0.002 |
| Smoking history, count (%) | 65 (20%) | 7 (14%) | 0.44 |
| NIHSS, median (IQR) | 16 (13–20) | 19 (16–23) | 0.001 |
| LKW-alteplase min, median (IQR) | 112 (85–157) | 120 (100–142) | 0.667 |
| IV alteplase, count (%) | 189 (57%) | 21 (43%) | 0.067 |
| Pre-EVT infarct Vol CC, median (IQR) | 23 (12–43) | 18 (9–26) | 0.137 |
| LKW-groin min, median (IQR) | 275 (187–376) | 255 (175–339) | 0.234 |

CC, cubic centimeters; IQR, interquartile range; LKW, last known well; NIHSS, NIH stroke scale; TIA, transient ischemic attack.

**Table 2** Outcomes after thrombectomy for patients with baseline modified Rankin Scale (mRS) dichotomized 0–1 vs 2–4

| | Baseline mRS 0–1 | Baseline mRS 2–4 | P value |
|---|---|---|---|
| TICI 2b–3, count (%) | 260 (78%) | 38 (78%) | 0.855 |
| ICH, count (%) | 23 (7%) | 1 (2%) | 0.340 |
| Final infarct vol CC, median (IQR) | 45 (18–116) | 68 (7–147) | 0.828 |
| 90-day absolute mRS ≤2, count (%) | 133 (45%) | 6 (14%) | <0.0001 |
| 90-day mortality | 55 (19%) | 21 (50%) | <0.0001 |
| 90-day delta mRS ≤0, count (%) | 48 (16%) | 10 (24%) | 0.272 |
| 90-day delta mRS ≤1, count (%) | 100 (34%) | 19 (45%) | 0.168 |
| 90-day delta mRS=1, count (%) | 52 (18%) | 9 (21%) | 0.524 |
| 90-day delta mRS ≤2, count (%) | 144 (49%) | 23 (55%) | 0.511 |
| 90-day delta mRS=2, count (%) | 44 (15%) | 4 (10%) | 0.480 |
| 90-day delta mRS=3, count (%) | 49 (17%) | 10 (24%) | 0.277 |
| 90-day delta mRS=4, count (%) | 37 (13%) | 9 (21%) | 0.145 |
| 90-day delta mRS=5, count (%) | 26 (8.8%) | 0 (0.0%) | 0.057 |

CC, cubic centimeters; ICH, intracerebral hemorrhage; IQR, interquartile range; TICI, thrombolysis in cerebral infarction.

**Table 3** Outcome associations with baseline ordinal modified Rankin Scale (mRS)

| | uOR (95% CI), uβ | P value | aOR (95% CI), aβ | P value |
|---|---|---|---|---|
| TICI 2b–3 | 0.914 (0.712 to 1.173) | 0.480 | 0.872 (0.545 to 1.396) | 0.569 |
| ICH | 0.521 (0.244 to 1.112) | 0.092 | 0.140 (0.016 to 1.230) | 0.076 |
| Final infarct vol (Ln CC) | −0.014 | 0.853 | 0.143 | 0.244 |
| 90-day absolute mRS ≤2 | 0.509 (0.370 to 0.700) | <0.0001 | 0.618 (0.345 to 1.105) | 0.104 |
| 90-day delta mRS ≤0 | 1.247 (0.943 to 1.648) | 0.121 | 1.541 (0.817 to 2.908) | 0.182 |
| 90-day delta mRS ≤1 | 1.149 (0.906 to 1.458) | 0.251 | 1.108 (0.666 to 1.844) | 0.694 |
| 90-day delta mRS ≤2 | 1.097 (0.869 to 1.386) | 0.436 | 1.187 (0.726 to 1.941) | 0.494 |

Adjusted for age, sex, vascular risk factors, NIH stroke scale score, and pre-thrombectomy infarct volume.
β, parameter estimate for linear regression; a, adjusted; CC, cubic centimeters; ICH, intracerebral hemorrhage; Ln, natural log; OR, odds ratio for logistic regression; TICI, thrombolysis in cerebral infarction; u, unadjusted.

## DISCUSSION

These data demonstrate that while there were differences between EVT patients with and without baseline disability, baseline disability did not detract from the relative benefit of EVT evaluated as accumulated disability (delta mRS) and was not associated with procedural complications. These data support a more inclusive EVT selection paradigm with regard to baseline disability, analogous to evidence suggesting patients with larger infarct cores may benefit from EVT.[15]

Patients with baseline disability were older, more likely to be female, had more preexisting vascular disease (coronary and stroke/TIA history), and higher NIHSS. The baseline characteristics of increased age and higher median NIHSS are aligned with prior comparisons of patients with and without pre-stroke disability.[16] The finding that those with baseline disability were more likely to be female concords with population-level data suggesting higher rates of disability in females than in males at older ages.[17 18] The propensity toward disability accumulation and frailty with advancing age in the general population likely explains the observed associations between age, baseline disability, and higher median NIHSS in patients presenting with acute stroke.[19 20] That patients with baseline disability are more likely to exhibit severe stroke-related deficits supports the propriety of aggressive efforts to salvage ischemic tissue, given higher rates of mortality and institutionalization with accumulated disability.[1 21]

While baseline mRS was associated with absolute 90-day mRS ≤2 in the unadjusted model, there was no association between baseline disability and accumulated disability, regardless of how this variable was dichotomized. Furthermore, baseline mRS was not associated with other outcomes, including reperfusion, ICH, and final infarct volume. These results are consistent with limited prior data indicating that patients with baseline disability experience similar rates of successful recanalization and ICH than those without baseline disability.[16 22] Recent observational data have added to the evidence base suggesting that baseline disability status does not significantly impact the likelihood of a return to prestroke functional level after EVT.[23] While baseline disability was associated with increased rate of post-stroke mortality,[23 24] we hypothesize that this association is more likely to arise from the unequal neurologic impact of stroke itself on vulnerable patients with baseline disability rather than from EVT. This association between stroke and mortality is likely further magnified in the counterfactual scenario where EVT is categorically withheld from patients with baseline disability. Further studies to identify characteristics associated with mortality in this population are needed. The lack of association between baseline disability and final infarct volume after EVT is a novel observation. While there is no mechanistic rationale to expect patients with baseline disability undergoing EVT to have larger acute infarct volumes than those without baseline disability, this lack of association further challenges the notion that patients with disability stand to benefit less from EVT. These considerations align with insights from observational studies of thrombolysis in patients with pre-stroke disability, where misguided concerns surrounding poor outcomes and treatment “futility” have been allayed by findings demonstrating greater likelihood of return to premorbid functional status with treatment despite preexisting disability.[25 26] While outcomes after stroke can be difficult to predict,[27] efforts to prevent accumulated disability are likely to be highly cost-effective given reductions in morbidity, nursing requirements, and long-term costs after stroke, in addition to quality of life benefits.[28–32] Indeed, growing evidence supports the importance of patients’ perspectives on quality of life.[33] Further evaluations investigating these additional outcomes are warranted.

This study has several limitations. Retrospective design introduces the risk of selection bias, as management decisions were at the discretion of treating clinicians. Therefore, patients with disability may be underrepresented in this study. Unfortunately, data for those not treated with EVT were not available. However, excluding disability status, baseline patient demographics, medical history, clinical presentation, and outcomes were similar to randomized EVT trials, underscoring generalizability.[12 34] While baseline mRS was reliably, prospectively recorded by certified staff for 83%, it was obtained by chart review for the remaining minority of patients. Similarly, MRI was available to reliably assess infarct volumes in just under half of patients (43% of pre-EVT MRIs and 44% of post-EVT MRIs). Another potential limitation is the timeframe spanning several practice-changing trials of EVT. Despite this, no significant associations of baseline mRS and TICI score or procedure complications were observed.

## CONCLUSIONS

The present data do not support the practice of routinely withholding EVT from patients on the sole basis of pre-existing disability, and indicate comparable rates of successful reperfusion, procedural complications, final infarct volume, and accumulated disability between patients with and without baseline disability. Treatment paradigms and policies that do not universally exclude patients with baseline disability are likely clinically and ethically appropriate, provided acute treatment is concordant with goals of care. Future stroke therapy trials designed with adjusted outcome measures, such as accumulated disability, cost-benefit analyses, and enrollment criteria that are inclusive of this historically underrepresented and vulnerable population of patients with disability are imperative.

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