Original research

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

Robert W Regenhardt, Michael J Young, Mark R Etherton, Alvin S Das, Christopher J Stapleton, Ammar Patel, Michael H Lev, Joshua A Hirsch, Natalia S Rost, Thabele M Leslie-Mazwi

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<0.001), 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). 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. While current American Stroke Association guidelines specify EVT “may be reasonable” for patients with prestroke disability, institutional policies and individual decisions to withhold treatment on the basis of prestroke disability remain common. 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.

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. 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 therapeutically approaches in persons with disabilities who experience stroke.

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
Parents who underwent anterior circulation EVT for large-vessel occlusion stroke were identified retrospectively from a prospectively maintained database 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). Baseline mRS was prospectively recorded in the database by clinical/research staff formally certified in mRS assessment for 83% of patients and by chart review blinded to outcome for the remainder. Baseline disability was defined as...
practical inability to perform the study without the waiver. Informed consent was waived based on minimal patient risk and this study was approved by the local institutional review board.

Analyses were performed with SPSS version 23.0 (IBM Corp, Armonk, New York, USA). 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. 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 (fivemRS=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 (20% 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=0.914, 95%CI=0.586 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=0.833, beta=−0.014), or ICH (P=0.092, OR=0.521, 95%CI=0.244–1.122). Adjusting for age, sex, vascular risk factors, NIHSS, and pre-EVT infarct volume did not significantly change these results (Table 3).

<table>
<thead>
<tr>
<th>mRS dichotomized 0–1 vs 2–4</th>
<th>Baseline mRS</th>
<th>Baseline mRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>68 (56–79)</td>
<td>81 (71–88)</td>
</tr>
<tr>
<td>Female, count (%)</td>
<td>161 (49%)</td>
<td>32 (65%)</td>
</tr>
<tr>
<td>Atrial fibrillation, count (%)</td>
<td>118 (36%)</td>
<td>18 (37%)</td>
</tr>
<tr>
<td>Diabetes, count (%)</td>
<td>66 (20%)</td>
<td>13 (27%)</td>
</tr>
<tr>
<td>Hypertension, count (%)</td>
<td>219 (66%)</td>
<td>37 (76%)</td>
</tr>
<tr>
<td>Coronary artery disease, count (%)</td>
<td>67 (20%)</td>
<td>19 (39%)</td>
</tr>
<tr>
<td>Stroke/TIA, count (%)</td>
<td>51 (15%)</td>
<td>17 (35%)</td>
</tr>
<tr>
<td>Smoking history, count (%)</td>
<td>65 (20%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>16 (13–20)</td>
<td>19 (16–23)</td>
</tr>
<tr>
<td>LWK-alteplase min, median (IQR)</td>
<td>112 (85–157)</td>
<td>120 (100–142)</td>
</tr>
<tr>
<td>IV alteplase, count (%)</td>
<td>189 (57%)</td>
<td>21 (43%)</td>
</tr>
<tr>
<td>Pre-EVT infarct Vol CC, median (IQR)</td>
<td>23 (12–43)</td>
<td>18 (9–26)</td>
</tr>
<tr>
<td>LWK-groin min, median (IQR)</td>
<td>275 (187–376)</td>
<td>255 (175–339)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>mRS dichotomized 0–1 vs 2–4</th>
<th>Baseline mRS</th>
<th>Baseline mRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TICI 2b–3, count (%)</td>
<td>260 (78%)</td>
<td>38 (78%)</td>
</tr>
<tr>
<td>ICH, count (%)</td>
<td>23 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Final infarct vol CC, median (IQR)</td>
<td>45 (18–116)</td>
<td>68 (7–147)</td>
</tr>
<tr>
<td>90-day absolute mRS ≤2, count (%)</td>
<td>133 (45%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>55 (19%)</td>
<td>21 (50%)</td>
</tr>
<tr>
<td>90-day delta mRS ≤0, count (%)</td>
<td>48 (16%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>90-day delta mRS ≤1, count (%)</td>
<td>100 (34%)</td>
<td>19 (45%)</td>
</tr>
<tr>
<td>90-day delta mRS=1, count (%)</td>
<td>52 (18%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>90-day delta mRS ≤2, count (%)</td>
<td>144 (49%)</td>
<td>23 (55%)</td>
</tr>
<tr>
<td>90-day delta mRS=2, count (%)</td>
<td>44 (15%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>90-day delta mRS=3, count (%)</td>
<td>49 (17%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>90-day delta mRS=4, count (%)</td>
<td>37 (13%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>90-day delta mRS=5, count (%)</td>
<td>26 (8.8%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

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

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

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likely explains the observed associations between age, baseline disabili-
tion and frailty with advancing age in the general population
after EVT. While baseline disability was associated with
impact the likelihood of a return to prestroke functional level
suggesting that baseline disability status does not significantly
Recent observational data have added to the evidence base
increased rate of post-
more likely to exhibit severe stroke-
disability, analogous to evidence suggesting patients with larger
infarct cores may benefit from EVT.

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 charac-
teristics of increased age and higher median NIHSS are aligned
with prior comparisons of patients with and without pre-stroke disability. 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. 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. 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 accumu-
lated disability.

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, regard-
less of how this variable was dichotomized. Furthermore, base-
line 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 reca-
ralization and ICH than those without baseline disability. 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. While baseline disability was associated with
increased rate of post-stroke mortality, we hypothesize that this association is more likely to arise from the unequal
effect 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 catego-
rically withheld from patients with baseline disability. Further studies to iden-
tify characteristics associated with mortality in this popu-
lation are needed. The lack of association between baseline
disability and final infarct volume after EVT is a novel observa-
tion. 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 pre-
exisiting disability. While outcomes after stroke can be diffi-
cult to predict, 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 addi-
tion to quality of life benefits. Indeed, growing evidence supports the importance of patients’ perspectives on quality
of life. 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. Unfortu-
nately, data on those not treated with EVT were not available.
However, excluding disability status, baseline patient demo-
graphics, medical history, clinical presentation, and outcomes
were similar to randomized EVT trials, underscoring general-
izability. 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 signifi-
cant 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 reperfu-
sion, procedural complications, final infarct volume, and accu-
mulated disability between patients with and without baseline
disability. Treatment paradigms and policies that do not univer-
sally exclude patients with baseline disability are likely clinically
and ethically appropriate, provided acute treatment is concor-
dant with goals of care. Future stroke therapy trials designed
with adjusted outcome measures, such as accumulated disability,

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>uOR (95% CI), uji</th>
<th>P value</th>
<th>aOR (95% CI), aji</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TICI 2b–3</td>
<td>0.914 (0.712 to 1.173)</td>
<td>0.480</td>
<td>0.872 (0.545 to 1.396)</td>
<td>0.569</td>
</tr>
<tr>
<td>ICH</td>
<td>0.521 (0.244 to 1.112)</td>
<td>0.092</td>
<td>0.140 (0.016 to 1.230)</td>
<td>0.076</td>
</tr>
<tr>
<td>Final infarct vol (Ln CC)</td>
<td>–0.014</td>
<td>0.853</td>
<td>0.143</td>
<td>0.244</td>
</tr>
<tr>
<td>90-day absolute mRS ≤2</td>
<td>0.509 (0.370 to 0.700)</td>
<td>&lt;0.0001</td>
<td>0.618 (0.345 to 1.050)</td>
<td>0.104</td>
</tr>
<tr>
<td>90-day delta mRS ≤0</td>
<td>1.247 (0.943 to 1.648)</td>
<td>0.121</td>
<td>1.541 (0.817 to 2.908)</td>
<td>0.182</td>
</tr>
<tr>
<td>90-day absolute mRS ≤1</td>
<td>1.149 (0.906 to 1.458)</td>
<td>0.251</td>
<td>1.108 (0.666 to 1.844)</td>
<td>0.694</td>
</tr>
<tr>
<td>90-day delta mRS ≤2</td>
<td>1.097 (0.869 to 1.386)</td>
<td>0.436</td>
<td>1.187 (0.726 to 1.941)</td>
<td>0.494</td>
</tr>
</tbody>
</table>

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.
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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Acknowledgements Joyce A McIntyre maintained the prospective Massachusetts General Hospital stroke database.

Contributors All authors have made significant contributions to this work. All have read and approved the final version of this manuscript.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval 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. Data are available upon reasonable request.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request and pending local IRB approval.

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