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Original research

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ABSTRACT

Background Analyses of the effect of pre-stroke functional levels on the outcome of endovascular therapy (EVT) have focused on the course of patients with moderate to substantial pre-stroke disability. The effect of complete freedom from pre-existing disability (modified Rankin Scale (mRS) 0) versus predominantly mild pre-existing disability/symptoms (mRS 1–2) has not been well delineated.

Methods The HERMES meta-analysis pooled data from seven randomized trials that tested the efficacy of EVT. We tested for a multiplicative interaction effect of pre-stroke mRS on the relationship between treatment and outcomes. Ordinal regression was used to assess the association between EVT and 90-day mRS (primary outcome) in the subgroup of patients with pre-stroke mRS 1–2. Multivariable regression modeling was then used to test the effect of mild pre-stroke disability/symptoms on the primary and secondary outcomes (delta-mRS, mRS 0–2/5–6) compared with patients with pre-stroke mRS 0.

Results We included 1764 patients, of whom 199 (11.3%) had pre-stroke mRS 1–2. No interaction effect of pre-stroke mRS on the relationship between treatment and outcome was observed. Patients with pre-stroke mRS 1–2 had worse outcomes than those with pre-stroke mRS 0 (adjusted common OR (acOR) 0.53, 95% CI 0.40 to 0.70). Nonetheless, a significant benefit of EVT was observed within the mRS 1–2 subgroup (cOR 2.08, 95% CI 1.22 to 3.55).

Conclusions Patients asymptomatic/without disability prior to onset have better outcomes following EVT than patients with mild disability/symptoms. Patients with pre-stroke mRS 1–2, however, more often achieve good outcomes with EVT compared with conservative management. These findings indicate that mild pre-existing disability/symptoms influence patient prognosis after EVT but do not diminish the EVT treatment effect.

INTRODUCTION

With the exception of MR CLEAN, the seminal trials of endovascular treatment (EVT) for acute ischemic stroke (AIS) excluded patients with pre-stroke disability, often defined as a modified Rankin Scale (mRS) score of ≥2.[1–5] Thus, there is a lack of evidence for this patient subgroup. Current guidelines suggest it may be reasonable to pursue thrombectomy in patients with pre-stroke mRS ≥2 if they fulfill certain criteria (eg, time of onset within 6 hours) as a level IIb recommendation, while level I recommendations for EVT remain restricted to patients with a pre-stroke mRS 0–1.[6] This has important implications for clinical practice, as up to one-third of patients with AIS may suffer from pre-existing disabilities.[7]

Several studies have been published on the effects of EVT on outcome for patients with pre-stroke disability, the majority of which provide no convincing evidence for a reduced treatment effect in these patient subgroups.[8–10] These studies were either observational or retrospective in nature, however, with varying inclusion criteria and outcome measures. As such, they require corroboration from higher quality data sources such as clinical trials. In addition, these analyses have all focused on the course of patients with moderate to substantial pre-stroke disability; the effect of the presence of any pre-stroke disability/symptoms versus none at all is not well delineated.

We aimed to compare the clinical outcomes and EVT treatment effect of patients with large vessel occlusion AIS with and without any (even mild) pre-existing disability or symptoms (mRS 1–2) on outcomes following EVT. The goals were to: (1) compare the clinical outcomes of the EVT and control arm patients according to their pre-stroke disability status (mRS 0 vs mRS 1–2) and (2) assess whether the effect of EVT differs between patients with and without any pre-existing disability or symptoms.

METHODS

Study population and design

The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration pooled individual patient data of seven randomized controlled trials that established EVT as a safe and effective treatment for patients with AIS (n=1764).[11] Of the included trials, only MR CLEAN permitted enrolment of patients with pre-stroke mRS ≥2 (n=45).[1] Detailed

methodology and inclusion criteria of the individual trials, as well as the HERMES meta-analysis, have been previously reported.[1–5 11–13] In brief, patients who were randomized to the control arm received standard medical care, including IV alteplase if eligible, while those randomized to the intervention arm underwent additional EVT. Patient consent was obtained unless the local boards allowed for deferral of consent.

Outcome measures

The primary outcome of interest was ordinal 90-day mRS. Secondary outcomes were change in mRS from baseline to 90 days (delta mRS, ordinal scale from −2, -1, 0, 1, 2, 3, 4, 5, 6), binarized good functional outcome (defined as mRS 0–2 at 90 days), binarized poor outcome (defined as mRS 5–6 at 90 days), and expanded Thrombolysis in Cerebral Infarction (eTICI) score (in the EVT arm only). The safety outcomes were mortality at 90 days and symptomatic intracerebral hemorrhage (sICH) at 24 hours.

Statistical analyses

We compared baseline characteristics of patients with and without any pre-stroke disability/symptoms using descriptive statistics and according to treatment arm.

Adjusted ordinal and binary logistic regression modeling was performed to measure the effect of mild pre-stroke disability/symptoms (binary variable mRS 1–2 yes/no) on the primary, secondary, and safety outcomes compared with patients who were asymptomatic/without disability prior to onset. Analyses were adjusted for treatment arm (EVT vs control), patient sex (binary), baseline National Institutes of Health Stroke Scale (NIHSS) score (continuous), administration of IV alteplase (binary), baseline Alberta Stroke Program Early CT Score (ASPECTS) (continuous), occlusion location (internal carotid artery (ICA) vs M1 segment of the middle cerebral artery (MCA) vs M2 segment of the MCA) (categorical), and time from onset to randomization (continuous). Logistic regression was used to test the multiplicative interaction effect of pre-stroke mRS (mRS 1–2 vs 0) and treatment (EVT vs control) on the primary, secondary, and safety outcomes.

As an exploratory analysis, univariable ordinal regression was performed to test the association between EVT and 90-day mRS within the subgroup of patients with predominantly mild pre-stroke disability or symptoms (mRS 1–2) and presented in comparison to those with no pre-existing symptoms or disability.

Missing data (including loss to follow-up) were minimal (less than 5%) for all outcomes and predictor variables used in the reported analyses, and hence no imputation was employed except for covariates in statistical modeling, for which simple imputation (median or mean) was used to avoid an undesirable reduction to complete-case analysis.

Unadjusted and adjusted (common) ORs are reported with 95% CIs. All statistical tests were two-sided, and a conventional significance threshold (alpha=0.05) was used for interpretation. Analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA) and R, version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

We used the STROBE cohort checklist when writing our report.[14]

RESULTS

Patient population

Of the 1764 patients included in the HERMES analysis, 199 (11.3%) had a pre-stroke mRS 1–2 (including 162 (81.4%) mRS 1, 37 (18.6%) mRS 2). Compared with pre-stroke asymptomatic patients, those with mild pre-stroke disability/symptoms undergoing EVT were older (median 70.2 vs 65.3 years, p=0.001), had higher rates of diabetes mellitus (23.5% vs 14.7%, p=0.036) and prior stroke (23.5% vs 9.5%, p<0.001), and less often received IV alteplase (75.5% vs 84.7%, p=0.038) (table 1). In the control arm, patients with pre-stroke mRS 1–2 were also older, less often received IV alteplase, and had overall higher rates of comorbidities (hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, and prior stroke) compared with patients with pre-stroke mRS 0 (table 1).

Interaction effect of pre-stroke mRS on the relationship between treatment and outcomes

No significant interaction was observed for pre-stroke mRS and treatment on any of the primary, secondary, or safety outcomes, suggesting homogeneity of treatment effect for patients with pre-stroke mRS 1–2 compared with those with pre-stroke mRS 0. Within the resulting exploratory analysis of the subgroup of patients with primarily mild pre-existing disability, those who underwent EVT more often achieved good outcomes compared with those who received conservative management (cOR 2.08, 95% CI 1.22 to 3.55; figure 1A). The effect size of EVT for those with pre-stroke mRS 0 on outcome was greater (cOR 2.22, 95% CI 1.78 to 2.75; figure 1B).

Comparison of patients with mild pre-stroke disability/symptoms versus patients with pre-stroke mRS 0

Patients with mild pre-stroke disability/symptoms had significantly lower rates of good 90-day functional outcomes (mRS 0–2) compared with those with pre-stroke mRS 0 (24.1% vs 39.2%) (table 2). Correspondingly, the rates of poor outcome (mRS 5–6, 39.7% vs 23.5%) and mortality at 90 days (28.1% vs 14.3%) were significantly higher in the patient group with pre-existing disabilities/symptoms (table 2). When looked at individually, patients with pre-stroke mRS 1 (n=162) had numerically slightly higher rates of good outcome (25.3% vs 18.9%) and successful reperfusion (78.9% vs 76.5%) with lower rates of poor outcome (39.5% vs 40.5%), mortality (26.5% vs 35.1%), and sICH (3.7% vs 8.1%) compared to those with pre-stroke mRS 2(table 3).

These results were reflected in logistic regression analyses. Compared with patients with pre-stroke mRS 0, patients who were symptomatic/mildly disabled prior to onset had overall worse 90-day outcomes (ordinal shift analysis: adjusted common OR (acOR) 0.53, 95% CI 0.40 to 0.70) and higher rates of mortality (aOR 1.83, 95% CI 1.23 to 2.71). Delta mRS (ie, the change in mRS from baseline to 90 days) was also higher in the pre-stroke mRS 1–2 group (acOR 2.57, 95% CI 1.95 to 3.41). The rates of sICH and successful reperfusion (EVT arm only) did not differ significantly between the two groups (table 2).

DISCUSSION

In this study, no interaction effect of pre-stroke mRS on treatment and outcome was observed. In other words, the effect of EVT treatment was not modified by pre-existing disability/symptoms. However, the presence of any (even mild) pre-stroke disability/symptoms was associated with poorer post-stroke outcomes.

To the best of our knowledge, this is one of the few studies that employed high quality data from randomized clinical trials to assess the effect of any pre-existing disability/symptoms in patients with AIS undergoing EVT on outcome; the majority of studies published to date have been observational and included those with moderate to substantial disability. For example, in

Table 1 Baseline characteristics of patients with mild pre-existing symptoms/disability (mRS 1–2) versus those with pre-stroke mRS 0, stratified according to treatment arm

	EVT			Control		
Characteristic	Pre-stroke mRS 1–2 Mean±SD (N) Median (IQR)	Pre-stroke mRS 0 Mean±SD (N) Median (IQR)	P value	Pre-stroke mRS 1–2 Mean±SD (N) Median (IQR)	Pre-stroke mRS 0 Mean±SD (N) Median (IQR)	P value
Age (years)	70.2±13.3 (98) 72.3 (60.6, 80.0)	65.3±13.0 (524) 67.0 (56.8, 76.0)	**0.001**	72.8±12.3 (101) 75.0 (67.0, 81.0)	65.4±12.8 (532) 66.9 (57.9, 75.0)	**<0.001**
Systolic blood pressure (mmHg)	146.8±26.1 (98) 143.0 (130.0, 163.8)	145.7±23.9 (524) 145.0 (130.0, 160.0)	0.677	145.0±25.9 (101) 144.0 (126.0, 160.0)	146.0±24.6 (533) 145.0 (129.0, 162.0)	0.700
Hypertension, % (n/N)	62.2% (61/98)	53.6% (281/524)	0.123	79.2% (80/101)	55.5% (296/533)	**<0.001**
Hyperlipidemia, % (n/N)	29.6% (29/98)	33.2% (174/524)	0.558	46.5% (47/101)	34.3% (183/533)	**0.024**
Diabetes mellitus, % (n/N)	23.5% (23/98)	14.7% (77/524)	**0.036**	24.8% (25/101)	16.1% (86/533)	**0.045**
Atrial fibrillation, % (n/N)	36.7% (36/98)	31.7% (166/524)	0.348	43.6% (44/101)	31.0% (165/533)	**0.015**
Prior stroke, % (n/N)	23.5% (23/98)	9.5% (50/524)	**<0.001**	21.8% (22/101)	9.4% (50/533)	**0.001**
Blood glucose (mg/dL)	133.1±35.3 (94) 122.1 (109.0, 145.3)	134.2±90.1 (516) 120.0 (106.2, 140.0)	0.906	133.4±50.1 (98) 120.6 (103.6, 146.5)	131.5±64.6 (527) 120.0 (105.5, 140.0)	0.780
NIHSS at baseline	17.5±5.1 (98) 17.0 (14.0, 20.8)	16.7±5.1 (521) 17.0 (13.0, 20.0)	0.143	17.0±5.4 (101) 17.0 (14.0, 21.0)	16.8±5.5 (532) 17.0 (13.0, 21.0)	0.683
ASPECTS at baseline	8.0±1.6 (97) 8.0 (7.0,9.0)	7.8±1.7 (520) 8.0 (7.0,9.0)	0.249	8.0±1.7 (100) 8.0 (7.0,9.0)	7.7±1.9 (524) 8.0 (7.0,9.0)	0.141
IV alteplase delivered, % (n/N)	75.5% (74/98)	84.7% (444/524)	**0.038**	81.2% (82/101)	88.9% (474/533)	**0.046**
Occlusion location, % (n/N)			0.441			0.190
ICA	28.3% (26/92)	29.9% (148/495)		26.8% (26/97)	31.1% (155/499)	
M1	57.6% (53/92)	60.4% (299/495)		68.0% (66/97)	59.3% (296/499)	
M2	14.1% (13/92)	9.7% (48/495)		5.2% (5/97)	9.6% (48/499)	
Other	0.0% (0/92)	0.0% (0/495)		0.0% (0/97)	0.0% (0/499)	
Collateral grade, % (n/N)			0.868			0.764
0	1.2% (1/86)	0.9% (4/466)		1.1% (1/89)	1.1% (5/473)	
1	14.0% (12/86)	10.5% (49/466)		13.5% (12/89)	14.0% (66/473)	
2	45.3% (39/86)	44.8% (209/466)		49.4% (44/89)	42.1% (199/473)	
3	39.5% (34/86)	43.8% (204/466)		36.0% (32/89)	42.9% (203/473)	
Onset to randomization	197.2±107.3 (98) 176.5 (128.5, 242.3)	216.6±101.0 (522) 200.5 (146.0, 260.0)	0.084	200.4±79.9 (101) 186.0 (140.0, 251.0)	216.0±94.7 (533) 199.0 (145.0, 275.0)	0.121
Onset to IV alteplase administration	113.4±45.6 (74) 100.0 (80.3, 135.0)	111.4±49.3 (442) 101.0 (75.0, 135.0)	0.741	121.3±72.8 (82) 107.5 (76.0, 134.8)	117.7±62.1 (475) 100.0 (75.0, 146.5)	0.634

ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular treatment; ICA, internal carotid artery; M1, M1 segment of the middle cerebral artery; M2, M2 segment of the middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

their two-center study, Salwi *et al* consecutively included 761 patients undergoing EVT, 259 (35%) of which had moderate pre-stroke disability (mRS 2–3).[8] No differences in the probability of maintaining pre-stroke functional status or rates of successful reperfusion were observed between those with moderate and those with no-to-minimal pre-stroke morbidity. The rate of 90-day mortality, however, was higher in patients with pre-stroke mRS 2–3. A recent analysis of the prospective multicenter MR CLEAN registry observed that a substantial proportion of patients with pre-stroke mRS 3–5 achieved either favorable outcome (mRS 0–2) or a return to baseline following EVT, with similar rates of complications to the pre-stroke independent population.[9] In this study, mortality rates differed according to the reason for pre-stroke dependence, data which was unfortunately unavailable for the HERMES cohort. Another study involving 84 pre-stroke dependent (mRS 3–5) patients found no differences in 90-day outcome, mortality, or rates of sICH following adjustment for potential confounders.[10] While generally in line with the results of the literature, a considerable strength of this study is the presentation of the control group, allowing for the determination of treatment effect. As expected, patients with pre-stroke mRS 1–2 had significantly higher rates of comorbidities compared with the entire HERMES patient population. Likely as a result, these patients also less frequently received IV alteplase. Although the majority of patients with pre-existing conditions/symptoms were categorized as pre-stroke mRS 1 (162/199, 81.4%), we observed worse outcomes and higher rates of mortality in this subgroup compared with those without any pre-stroke disability/symptoms. This was true despite there being no differences in the rates of successful reperfusion (for those who underwent EVT) or sICH. The absolute difference between pre- and post-stroke mRS (delta mRS) was higher in the pre-stroke mRS 1–2 group due to the fact that these patients more often experienced worse outcomes (and thus a greater increase in points on the mRS scale) compared with those with pre-stroke mRS 0. Importantly, however, within the subgroup of patients with pre-existing disability/symptoms, a

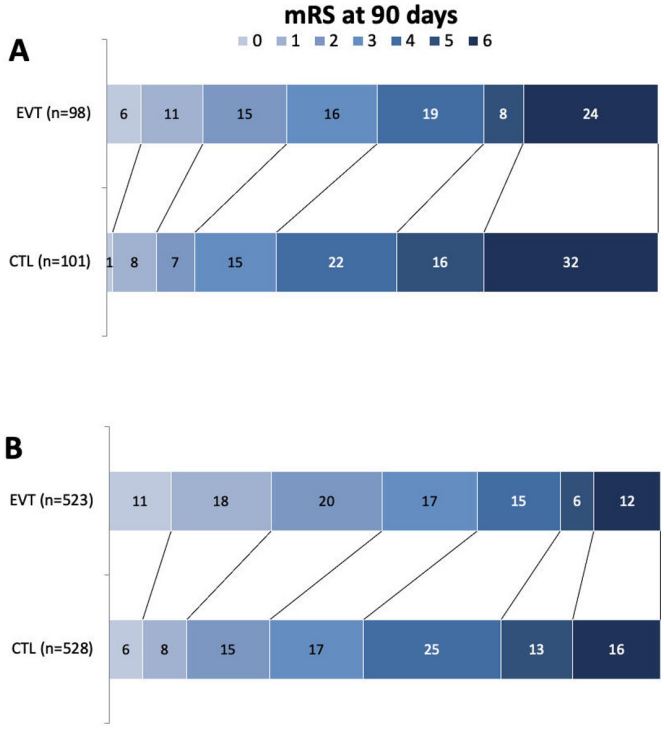

Figure 1 Distribution (in percentage) of mRS scores at 90 days in the intervention and control arms for patients with predominantly mild pre-stroke disability/symptoms (mRS 1–2 (A) and those with pre-stroke mRS 0 (B). mRS, modified Rankin Scale; EVT, endovascular treatment; CTL, control.

significant benefit of EVT was observed, these patients overall faring better than those who received standard care alone.

While the application of a particular treatment to clinical practice is usually based on the results (and therefore the inclusion criteria) of randomized clinical trials, those criteria should not be overly restrictive. A balance between trial and real-world conditions must be achieved to avoid unfair exclusion of patients who may otherwise benefit from treatment, particularly if the condition is severely disabling and if no comparable alternative treatment options exist. In the HERMES meta-analysis, the positive effect of EVT on outcome was maintained across multiple pre-specified subgroups, including patients of either sex, aged >80 years, those randomized more than 5 hours after symptom onset, and those who did not receive IV alteplase.[11] Trials on other subgroups, such as those with low ASPECTS (LASTE, ClinicalTrials.gov Identifier: NCT03811769), low baseline NIHSS (ENDOLOW, ClinicalTrials.gov Identifier: NCT04167527; MOSTE, ClinicalTrials.gov Identifier: NCT03796468), and medium vessel occlusions (ESCAPE-MeVO, ClinicalTrials.gov Identifier: NCT05151172) have either been initiated or are currently underway, with an increasing amount of supportive evidence being generated from observational prospective and retrospective studies, including those involving patients with pre-stroke disability.[8 10 15–20] This suggests that EVT is already being applied to a heterogenous population in clinical practice, which is required before we can examine its true effect on the broader population of patients with AIS. Pre-stroke disability, however, remains a complex matter. The mRS was originally developed to assess patients post-stroke[21] and, although widely used as an assessment tool in the pre-stroke setting, it is not without its pitfalls. Due to time constraints, as well as the nature of stroke symptoms with patients often unable to communicate, physicians are frequently forced to make quick judgements with limited or potentially even inaccurate information coming from patient medical records.[22 23] This can result in uncertainty that leads to the withholding of treatment. Falsely categorizing a patient as pre-stroke mRS 3 when he or she is in reality mRS 2 can therefore have grave consequences. On the other hand, the distinction between pre-stroke mRS 0 and mRS 1 may not have a bearing on treatment decision-making; these patients can function independently and the onset of an acute stroke should lead them to care regardless.

Table 3 Primary, secondary, and safety outcomes stratified by mRS category for patients with pre-stroke disability/symptoms

	% (n/N)	
Outcome	**Pre-stroke mRS 1**	**Pre-stroke mRS 2**
mRS 0–2 at 90 days	25.3% (41/162)	18.9% (7/37)
mRS 5–6 at 90 days	39.5% (64/162)	40.5% (15/37)
Mortality at 90 days	26.5% (43/162)	35.1% (13/37)
sICH at 24 hours	3.7% (6/162)	8.1% (3/37)
eTICI 2b/3 post-procedure	78.9% (56/71)	76.5% (13/17)

eTICI, expanded Thrombolysis in Cerebral Infarction score; mRS, modified Rankin Scale; sICH, symptomatic intracerebral hemorrhage.

Table 2 Primary, secondary, and safety outcomes for patients with pre-existing symptoms/disability (mRS 1–2) compared with patients with pre-stroke mRS 0

	% (n/N)		Unadjusted			Adjusted		
Outcome	**Pre-stroke mRS 1–2**	**Pre-stroke mRS 0**	**(c)OR**	**95% CI**	**P value**	**(c)OR**	**95% CI**	**P value**
mRS at 90 days	–	–	0.47*	0.36 to 0.62	<0.001	0.53*	0.40 to 0.70	<0.001
Delta mRS at 90 days†	–	–	1.89*	1.45 to 2.48	<0.001	2.57*	1.95 to 3.41	<0.001
mRS 0–2 at 90 days	24.1% (48/199)	39.2% (412/1051)	0.47	0.33 to 0.68	<0.001	0.50	0.34 to 0.74	0.001
mRS 5–6 at 90 days	39.7% (79/199)	23.5% (247/1051)	2.17	1.57 to 3.00	<0.001	1.65	1.15 to 2.38	0.007
Mortality at 90 days	28.1% (56/199)	14.3% (150/1051)	2.38	1.66 to 3.39	<0.001	1.83	1.23 to 2.71	0.003
sICH at 24 hours	4.5% (9/199)	4.3% (45/1057)	1.08	0.51 to 2.25	0.847	0.88	0.41 to 1.89	0.742
eTICI 2b/3 post-procedure	78.4% (69/88)	76.3% (354/464)	1.12	0.63 to 1.98	0.708	1.04	0.58 to 1.86	0.908

*Common OR derived from ordinal regression.
†Delta mRS is the ordinal degree of change in mRS from pre-stroke to 3 months post-stroke. The negative effect of pre-stroke disability/symptoms on outcome compared with that of patients with pre-stroke mRS 0 is greater than the baseline differences in mRS between the two groups.
eTICI, expanded Thrombolysis in Cerebral Infarction score; mRS, modified Rankin Scale; sICH, symptomatic intracerebral hemorrhage.

Furthermore, there may be subconscious biases associated with pre-stroke disability that affect treatment decision-making, as explored by Young *et al*.[24] These include ineffectual bias (eg, underestimating the quality of life or competence of persons with disability), fragility bias (eg, that such patients are more prone to complications/risks of a particular treatment), and catastrophe bias (eg, the presumption of lower resilience/greater subjective suffering of disabled patients).[25] Finally, as well as the degree of disability, the temporal nature (transient vs permanent) is also important, with patients with temporary symptoms or disability more likely to have a better prognosis.

Taken together with the results of this study and others, it becomes clear that a substantial amount of uncertainty exists around the importance of pre-stroke disability for EVT decision-making. In contrast to the strict inclusion criteria of the clinical trials, treatments are often offered to a broader patient population in the clinical routine. Due to the homogeneity of the effect of EVT for patients with and without mild pre-stroke disability/symptoms, care should be taken to avoid being overly restrictive.

Study limitations

This study has several limitations. First, the mRS may not be an appropriate assessment tool for pre-stroke disability; we were unable to internally validate the pre-stroke mRS scores with other similar scales such as the Barthel Index, which may have increased our confidence in the accurate scoring of the patients' conditions. We nevertheless chose the mRS to define pre-stroke disability since it is the most widely used measure to describe pre- and post-stroke disability. Second, because functional outcome is independently associated with pre-existing disability, the comparative value of functional outcomes with those from pre-stroke independent patients may be limited. Third, due to the strict inclusion criteria of the randomized clinical trials, our sample size of patients with pre-stroke disability/symptoms is limited. To avoid overfitting, we present unadjusted ordinal regression results of the effect of EVT versus control on outcome in the pre-stroke mRS 1–2 subgroup. Fourth, although we collected extensive baseline data including the assessment of multiple comorbidities, the causes for pre-stroke mRS were unknown. Knowing this information could help further tease apart patients most likely to benefit from EVT. Finally, while we did not observe a difference in the final rates of successful reperfusion, the rates of eTICI 2b/3 first-pass effect, which is known to be associated with clinical outcome, mortality, and sICH,[26 27] were not available. As a result, we are unable to comment on whether this differed between the two groups. This would be interesting information from a treatment decision-making standpoint and should be considered in future studies involving patients with pre-stroke disability/symptoms.

CONCLUSIONS

Patients who are completely disability- or symptom-free prior to their stroke have better outcomes following EVT than those with mild pre-stroke disability or symptoms. However, no interaction effect of pre-stroke mRS on treatment and outcome was observed; the effect of EVT is similar in patients with and without pre-stroke disability/symptoms, as are reperfusion rates and sICH. These findings indicate that even mild pre-existing conditions are prognostic (outcome) but not predictive (different response to therapy) in patients eligible for EVT.

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