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ORIGINAL COMMUNICATION

Misjudgment of pre-stroke functional status contradicts beneficial outcomes after endovascular therapy for large vessel occlusion

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Abstract

Endovascular therapy (EVT) trials enrolled ischemic stroke patients with good pre-stroke functional status. However, this information needed for rapid decision-making is commonly lacking in clinical practice. We hypothesized that initial misjudgment of pre-stroke functional status attenuates clinical outcomes of EVT. Data were derived from our prospective registry of ischemic stroke patients undergoing EVT for anterior circulation large vessel occlusion (01/2016–12/2017). Considering all information accumulated during hospital course, pre-stroke modified Rankin scale (mRS) was independently re-assessed and compared with pre-EVT assessments. Misjudgment was defined as any difference in mRS categories between first- and second-look assessments. Multivariable model was built to adjust for confounding variables of unfavorable outcome (mRS 3–6) and death at 90 days. Overall, we studied 217 patients: median age 75 years (IQR 64–81), 54% women, median NIHSS 17 (12–20) points. Second-look assessment of pre-stroke mRS revealed 73 (34%) cases initially being misjudged by ≥ 1 category and 17 (8%) by ≥ 2 categories. None of the second-look mRS assessments resulted in a lower mRS category than initially rated. Patients whose pre-stroke mRS score was misjudged prior to EVT showed more frequently unfavorable outcome (62/73 [84.9%] vs. 94/144 [65.3%], $p = 0.002$) or were deceased (30/73 [41.1%] vs. 25/144 [17.4%], $p < 0.001$) at 90 days than patients with consistent mRS assessments. Moreover, unfavorable outcomes occurred in nearly all patients whose initial mRS was misjudged by ≥ 2 categories (mRS 3–6: 17/17 [100%]; death: 14/17 [82.4%]; $p < 0.001$). In conclusion, thorough pre-EVT assessment of pre-stroke functional status appears decisive for proper selection of EVT candidates.

Keywords Acute ischemic stroke · Endovascular therapy · Pre-stroke functional status · Functional outcome

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Introduction

Pivotal randomized trials have proven efficacy of endovascular therapy (EVT) in ischemic stroke patients with anterior circulation large vessel occlusion [1]. The most recent DAWN and DEFUSE-three trials further provided clear evidence that patients even treated in an extended time window up to 24 h from symptom onset may benefit from EVT [2, 3]. Nonetheless, these trials selected patients according to their pre-stroke functional status. Functional independency was expressed by modified Rankin scale (mRS) scores of equal to or less than one and was a prerequisite for further consideration in most of these trials [1]. Consequently, the American Heart Association (AHA) guidelines adopted pre-stroke mRS ≤ 1 as an eligibility criterion for EVT [4]. In daily practice, however, sufficient information on pre-stroke functional status is commonly lacking mostly due to absence of patients' family members or acquaintances limiting its valid determination as shown previously [5, 6]. Furthermore, time-sensitivity of the disease complicates in-depth determination of pre-stroke functional status and quick assessment by emergency personnel may be prone to overestimate actual functional status pre-ictus.

We therefore hypothesized that initial misjudgment of pre-stroke functional status could account for unfavorable outcomes in ischemic stroke patients undergoing EVT for anterior circulation large vessel occlusion, despite favorable imaging profiles and optimized process times pre-treatment.

Methods

Study design and study population

We conducted an observational study based on our ongoing prospective EVT registry of consecutive ischemic stroke patients ≥ 18 years undergoing EVT for large vessel occlusion. For this analysis, we solely used data from patients with anterior circulation stroke treated between January 2016 and December 2017. Patients were admitted either directly through the emergency department of our tertiary neurovascular center, were transferred via our hub-and-spoke telestroke network (SOS-TeleNet) or were transferred from other remote hospitals not linked to our telestroke network. At our neurovascular center, patients routinely underwent non-contrast CT and CT-angiography (CTA) and were deemed eligible for EVT if the following evidence-based criteria were met: (1) time window ≤ 6 h (modified to ≤ 24 h after publication of DAWN and DEFUSE-3 trials); (2) admission CT ASPECTS ≥ 6 points; (3) CTA evidence of symptomatic intracranial occlusion of middle cerebral (MCA) and/or internal carotid artery (ICA); and (4) in selected cases, evidence of potentially beneficial CT-perfusion maps and/or beneficial collateral circulation on CTA [1–3]. The decision whether to perform EVT was made by the stroke neurologists and neurointerventionalists on service.

Our prospective registry contains data on demographics (i.e., age, sex), clinical (i.e., past vascular risk factors, admission National Institutes of Health Stroke Scale [NIHSS] scores), imaging (i.e., admission Alberta Stroke Program Early CT Score [ASPECTS], occlusion site,) and treatment (intravenous thrombolysis, modified Thrombolysis in Cerebral Infarction [mTIBI] score post-EVT) variables as well as pre- and intra-hospital process times. Modified Rankin scale scores were prospectively assessed at 90 days per phone interview. Clinical endpoints used in this study comprised unfavorable outcome (defined as mRS 3–6) and death at 90 days.

Assessment of pre-stroke functional status

Pre-stroke functional status was obtained prior to EVT procedure as standard-of-care according to all information gathered by emergency personnel involved in initial patient evaluation (i.e., emergency medical services, emergency department staff, admitting physician at remote hospital, telestroke physician, stroke team at neurovascular center). For this analysis, two independent raters (A.P., C.G.) experienced in stroke care and mRS scoring reviewed all patient-related data that were available at the time of EVT decision-making and determined pre-stroke mRS (i.e., first-look assessment). As a second step, all data on patients' functional status prior to the stroke that further accumulated during hospital course including detailed information gathered from patients themselves, their family members and/or acquaintances and family physicians or other outpatient medical personnel were independently interpreted to re-classify pre-stroke mRS (i.e., second-look assessment). Second-look assessments were blinded to results from first-look assessments and conducted by the same raters. Disagreements between both raters were resolved independently by a referee rater (K.B.). We defined misjudgment of initial pre-stroke functional status as any difference in the mRS categories that occurred between first-look and second-look assessments.

Statistical analysis

Statistical analyses were performed with STATA software (version 12.1, StataCorp. College Station, TX). Continuous variables are presented as mean ± standard deviation

(SD) for normally distributed and as median (interquartile range, IQR) for skewed data. Non-continuous variables are presented as percentages. Statistical comparisons were performed using Chi-square test, Fisher´s exact test, Student´s *t* test and Wilcoxon rank-sum, where appropriate. A multivariable model was built to adjust for a fixed set of known predictors of unfavorable outcome (mRS 3–6) and death at 90 days [7].

We computed Cohen-weighted kappa (κ) to assess the inter-rater reliability for both first-look and second-look assessments of the pre-stroke functional status by comparing the results of the two raters, where κ values ≤ 0.20 were considered slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.81–1.00 almost perfect agreement[8]. To evaluate the intra-rater repeatability for first-look and second-look assessments, both raters independently performed a blinded re-assessment of 20 randomly selected first-look and second-look mRS scores 4–6 weeks after the initial assessments.

Results

During the 2-years observational period, a total of 217 consecutive ischemic stroke patients who underwent EVT for anterior circulation large vessel occlusion were included into this analysis. Of these, 76 (35%) patients were directly admitted to our neurovascular center and 141 (65%) were transferred from either telestroke hospitals (65 [30%]) or remote hospitals not linked to our telestroke network (76 [35%]). The median age of the study population was 75 (64–81) years and 118 (54.3%) were female. The admission median NIHSS score was 17 (12–20) points and median ASPECT score was 7 (6–8) points. Intravenous tPA was administered in 139 (64.1%) patients.

Pre-stroke mRS scores could be determined for all patients. No missing data occurred with regard to 90-days outcomes. First-look and second-look ratings on pre-stroke mRS scores are summarized in Table 1. By comparing first-look with second-look assessments of the pre-stroke functional status, pre-stroke mRS was misjudged in 73/217 (33.6%) patients. In 56/217 (25.8%) patients, pre-stroke mRS score was misjudged by one category and in 17/217 (7.8%) patients by two or more categories. None of the second-look mRS assessments resulted in a lower mRS category than initially rated, in other words, all misjudged first-look mRS scores were falsely low (Table 1). Considering dichotomous mRS categories, 27 of 217 (12.4%) patients who were initially allocated to an mRS ≤ 1 had actual higher mRS (>1) scores in re-assessments.

Baseline characteristics of patients with consistent compared to misjudged pre-EVT mRS scores are in Table 2. Patients with misjudged mRS scores were older (79 vs. 74 years), suffered more frequently from diabetes mellitus (45% vs. 23%) and atrial fibrillation (69% vs. 49%) and received less frequently intravenous tPA (52% vs.70%) than patients with consistent mRS assessments ($p<0.05$). Any misjudgment of the initial pre-stroke functional status was not associated with mode of admission (direct admission, 34.2%; telestroke transferal, 36.9%; non-telestroke-transferal, 30.3%; $p=0.7$).

Compared to patients with consistent mRS score assessments, patients with misjudged mRS score assessment prior to EVT more frequently had unfavorable outcome [62/73 (84.9%) vs. 94/144 (65.3%), $p=0.002$] or were deceased [30/73 (41.1%) vs. 25/144 (17.4%), $p<0.001$] at 90 days. No difference was present regarding major reperfusion post-EVT [53/73 (72.6%) vs. 113/144 (78.5%), $p=0.34$). Unfavorable outcomes occurred in nearly all patients whose initial mRS score was misjudged by ≥ 2 categories [mRS score 3–6: 17/17 (100%); death: 14/17 (82.4%); $p<0.001$].

In multivariable analysis adjusting for a fixed set of factor variables based on literature (i.e., age, admission NIHSS, admission ASPECTS, intravenous tPA, occlusion site, onset-to-groin puncture time and reperfusion status post-EVT), any misjudgment of the pre-stroke functional status emerged as an independent predictor of unfavorable outcome (adjusted OR 2.52; 95% CI 1.03–6.17; $p=0.043$) and death (adjusted OR 2.47; 95% CI 1.21–5.08; $p=0.013$) at 90 days.

Table 1 Agreement between first-look and second-look assessment of the pre-stroke mRS

		Second-look mRS						
		0	1	2	3	4	5	Total
First-look mRS	0	118	43	4	3	–	–	168
	1	–	14	14	8	–	–	36
	2	–	–	6	2	2	–	10
	3	–	–	–	–	2	–	2
	4	–	–	–	–	–	1	1
	5	–	–	–	–	–	–	–
	Total	118	57	24	13	4	1	217

mRS indicates modified Rankin Scale

Table 2 Baseline characteristics of patients with consistent and misjudged pre-morbid mRS scores

	Consistent mRS ($n=144$)	Misjudged mRS ($n=73$)	p value
Age, median (IQR)	74 (63–80)	79 (73–85)	<0.0001
Women, *n* (%)	67 (46.5)	32 (43.8)	0.71
Past vascular risk factors, *n* (%)			
Arterial hypertension	124 (86.1)	67 (91.8)	0.22
Hyperlipidemia	42 (29.2)	21 (28.8)	0.35
Diabetes mellitus	33 (22.9)	33 (45.2)	0.001
Atrial fibrillation	70 (48.6)	50 (68.5)	0.005
Tobacco use	9 (6.3)	1 (1.4)	0.17*
Previous stroke/TIA	20 (13.9)	11 (15.1)	0.82
Baseline NIHSS, median (IQR)	16 (12–19)	17 (14–21)	0.11
Baseline ASPECTS, median (IQR)	7 (6–8)	8 (6–8)	0.07
Occlusion site, *n* (%)			0.94*
M1-middle cerebral artery	104 (72.2)	52 (71.2)	
M2- middle cerebral artery	7 (4.9)	3 (4.1)	
Carotid-T-/L-occlusion	33 (22.9)	18 (24.7)	
Intravenous thrombolysis, n (%)	101 (70.1)	38 (52.1)	0.009
Process times, min, median (IQR)			
Onset-to-needle	109 (90–145)[a]	117 (83–136)[b]	0.87
Door-to-needle	44 (35–60)[c]	47 (35–59)[a]	0.89
Onset-to-groin	253 (180–324)[d]	275 (199–325)[e]	0.44
Picture-to-puncture	57 (45–78)	60 (44–80)	0.74

IQR indicates interquartile range, *NIHSS* National Institute of Health Stroke Scale, *mRS* modified Rankin Scale, *EVT* endovascular thrombectomy, *TIA* transient ischemic attack, *ASPECTS* Alberta Stroke Program Early CT Score

*Fisher's Exact Test

[a]Missing data for six patients

[b]Missing data for one patient

[c]Missing data for three patients

[d]Missing data for 12 patients

[e]Missing data for seven patients

Disagreements between the two raters on the assessments of first-look and second-look mRS scores were present in 13 and 20 cases, respectively. The inter-rater reliability was almost perfect between the two raters for both first-look (κ_w: 0.86; 95% CI 0.81–0.88) and second-look (κ_w: 0.90; 95% CI 0.85–0.92) assessments of the pre-morbid mRS. Repeated assessments on first- and second-look pre-stroke mRS showed substantial agreement for both rater 1 (κ_w: 0.64; 95% CI 0.00–0.74 and κ_w: 0.73; 95% CI, 0.57–0.87, respectively) and rater 2 (κ_w: 0.70; 95% CI 0.47–0.79 and κ_w: 0.61; 95% CI, 0.17–0.82, respectively).

Discussion

Our observational analysis showed that in patients with anterior circulation large vessel occlusion deemed candidates for EVT, emergently assessed pre-stroke functional status frequently does not reflect actual functional status pre-stroke, and initial misinterpretation of pre-stroke functional status lowers chances of beneficial outcomes after EVT despite favorable baseline imaging and clinical profiles.

The mRS score is widely used to assess pre-stroke functional status in both clinical research and clinical practice. Current AHA stroke guidelines state pre-stroke mRS ≤ 1 as an entry criterion for EVT [4]. However, sole consideration of mRS for assessing pre-stroke functional status appears questionable [9]. Based on information available prior to EVT, pre-stroke mRS score was misjudged in more than one-third of all patients in our analysis. Therefore we may conclude that the significance of this scale for determining pre-stroke function is limited, at least in the acute phase of stroke where timely decision making is essential for treatment [10]. This conclusion is corroborated by an analysis of the Anglia Stroke Clinical Network Evaluation Study (ASCNES) comprising 2491 stroke patients that showed only moderate validity of the mRS in assessment of pre-stroke functional status [5]. Similarly, Fearon et al. demonstrated

poor correlation between mRS and certain markers of pre-stroke functional ability such as comorbidity and frailty in patients admitted to a stroke center [6]. Validity of this scale might be even lower in the acute setting of stroke, where in-depth assessment of functional abilities as specified by structured mRS interview is not practicable and required information on a variety of domains of activities of daily living are rarely available. An explanation that has been repeatedly emphasized is that the mRS was originally designed to assess post-stroke recovery rather than functional status pre-stroke as the questionnaire specifically asks for functional abilities compromised after an index stroke [5, 6, 11].

Given current AHA guideline recommendations, underestimation of pre-stroke function might withhold patients from being considered for EVT or enrolment into clinical trials [2]. In a recent prospective cohort study, 30.5% of consecutive 1607 stroke patients were found to have pre-stroke disability (mRS > 1) that theoretically would have excluded them from receiving an evidence-based therapy or enrolment into a clinical trial [12]. In our cohort, however, none of the second-look assessments of pre-stroke mRS scores suggested lower degree of functional dependency than initially assumed prior to EVT. On the contrary, 12.4% of our patients converted from mRS ≤ 1 to mRS > 1 category in re-assessments. Functional status pre-stroke, therefore, might play a subordinate role in real-world EVT decision-making process as stroke physicians are rather tending to treat given the unfavorable natural course of patients with large vessel occlusive stroke. On the other hand, overestimating pre-stroke functional status might diminish expectations on functional outcomes after EVT as suggested by our data. Patients whose pre-stroke mRS scores were rated falsely low had worse outcomes than patients with consistent mRS assessments (85% versus 65%). Although functionally dependent patients were mostly excluded from pivotal stroke trials [1, 13], the observation that patients with pre-stroke dependency have lower chances of achieving beneficial outcomes than previously independent patients is not new. Registry data from 14,437 stroke patients showed that higher pre-stroke mRS scores were associated with greater risk of mortality [14] Aside from mortality, pre-stroke mRS also emerged as negative prognostic indicator of stroke outcomes such as length of hospital stay, post-stroke complications and discharge destination in an analysis of the ASCNES data set [4]. Stroke patients who received intravenous thrombolysis carried higher mortality risk when they were functionally dependent compared with previously independent patients [15].

The options to obtain sufficient information on pre-stroke functional status are limited, as gathering of such does not constitute a top priority in the acute stroke setting. Nevertheless, a standardized approach in the physician first-contact patient setting could be an attempt to overcome possible misinterpretation of pre-stroke functional status and estimate patients' expectations of recovery from a stroke in a more realistic way. Although contrary to guideline recommendations, it may not be justified to withhold EVT in most previously dependent patients as some may still benefit from reperfusion therapies, perhaps reflected by outcome measures others than mRS (e.g., health-related quality of life) [16]. However, while treatment decisions in patients directly admitted to EVT-capable hospitals are less likely influenced by such considerations, risk–benefit estimations should be taken into account in patients who are considered for inter-hospital transfers given enormous logistic efforts and resources needed.

Limitations associated with our analysis include the monocentric design and its limited external validity. Also, first-look and second-look assessments were conducted in retrospect and subject to availability of according information on pre-stroke functional status in patients' case records [17]. Also, some of the initial patient reports were documented by internists (as one-third of patients were transferred from telestroke hospitals), so that physical examination and visual inspection may differ from those of neurologists. This might have skewed our results, yet it somewhat reflects clinical real-world practice in acute stroke setting where comprehensive information on this matter is seldom available. Since we had no reference standard to compare, it remains unanswered whether re-assessments of pre-stroke mRS scores were more valid than first-look assessments and vice versa. Although we employed blinded raters experienced in mRS grading, the finally concluded mRS grades could be still biased due to the subjective nature of the assessment itself. Lastly, since we only report on patients who ultimately underwent EVT, we cannot conclude how many patients were withheld from EVT due to pre-existing functional dependency.

In conclusion, precise assessment of pre-stroke functional status should be considered in stroke patients deemed candidates for EVT, not only to determine EVT-eligibility according to evidence-based guideline recommendations, but also to estimate stroke outcome expectations realistically.

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Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical standards The study has been approved by the institutional research ethics committee of the Technische Universität Dresden (#272,072,017) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Since we used observational data from an ongoing registry informed formal consent was not required; however,

patients or their legally authorized representatives gave approval for treatment with intravenous thrombolysis and/or EVT, where possible.

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