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Predictors of return to pre-stroke function after reperfusion therapy in patients with premorbid disability – a post-hoc analysis of the Czech Registry

Prediktory návratu k pre-iktovému funkčnímu stavu po reperfuzní léčbě u pacientů s premorbidní disabilitou: post-hoc analýza českého registru

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Abstract

Background and objectives: The eligibility of acute ischemic stroke (AIS) patients with pre-existing neurological disability (modified Rankin Scale [mRS] ≥ 3) for acute reperfusion therapy remains uncertain. The aim was to identify factors predicting the return to their baseline functional status after reperfusion therapy in AIS patients with premorbid disability (pre-stroke mRS ≥ 3). *Methods:* We analyzed data from patients with premorbid disability from the Czech national registry for intravenous thrombolysis/endovascular treatment (2016–2020). The primary outcome was return to baseline mRS (ΔmRS = 0) at 3 months. Using multivariate logistic regression, we identified predictors of this outcome. *Results:* Among 1,712 patients, 32.1% (275/857) returned to their baseline status. Independent predictors of successful return included: age (adjusted odds ratio [aOR] 0.97 per year, 95% confidence interval [CI] 0.95–0.98), baseline National Institutes of Health Stroke Scale (NIHSS) (aOR 0.94 per point, 95% CI 0.92–0.96), absence of atrial fibrillation (aOR 0.78, 95% CI 0.63–0.97), and onset-to-treatment time (aOR 0.99 per minute, 95% CI 0.98–0.99). Patients with premorbid mRS 3 were more likely to return to baseline than those with an mRS 4–5 (aOR 1.42, 95% CI 1.18–1.67). Reperfusion was more effective in patients with atherothrombotic stroke etiology (aOR 1.69, 95% CI 1.31–2.14) compared to cardioembolic etiology (aOR 1.21, 95% CI 0.95–1.53). *Discussion:* Younger age, lower NIHSS, absence of atrial fibrillation, atherothrombotic etiology, and faster treatment commencement are key predictors of regaining baseline functional status after reperfusion in AIS patients with premorbid disability.

Souhrn

Východiska a cíle: Způsobilost pacientů s akutní ischemickou CMP (iCMP) s premorbidní disabilitou (pre-iktová modifikovaná Rankinova škála [mRS] ≥≥ 3) pro akutní reperfuzní terapii zůstává nejistá. Cílem bylo identifikovat faktory předpovídající návrat k původnímu funkčnímu stavu po reperfuzní terapii u pacientů s akutní iCMP s premorbidní disabilitou (pre-iktová mRS ≥ 3). *Metody:* Analyzovali jsme data pacientů s premorbidní disabilitou z českého národního registru pro intravenózní trombolýzu/endovaskulární léčbu (2016–2020). Primárním výstupem byl návrat k výchozí mRS (ΔmRS = 0) ve 3 měsících. Pomocí multivariátní logistické regrese jsme identifikovali prediktory tohoto výsledku. *Výsledky:* Z 1 712 pacientů se 32,1 % (275/857) vrátilo k výchozímu stavu. Nezávislými prediktory úspěšného návratu byly: věk (adjusted odds r atio [aOR] 0,97 na rok, 95% interval spolehlivosti [CI] 0,95–0,98), výchozí National Institutes of Health Stroke Scale (NIHSS) (aOR 0,94 na bod, 95% CI 0,92–0,96), nepřítomnost fibrilace síní (aOR 0,78, 95% CI 0,63–0,97) a čas od vzniku příznaků do zahájení léčby (aOR 0,99 na minutu, 95% CI 0,98–0,99). Pacienti s premorbidním mRS 3 se s větší pravděpodobností vrátili k výchozímu stavu než pacienti s mRS 4–5 (aOR 1,42, 95% CI 1,18–1,67). Reperfuze byla účinnější u pacientů s aterotrombotickou etiologií iktu (aOR 1,69, 95% CI 1,31–2,14) ve srovnání s kardioembolickou etiologií (aOR 1,21, 95% CI 0,95–1,53). *Diskuze:* Nižší věk, nižší NIHSS, nepřítomnost fibrilace síní, aterotrombotická etiologie a rychlejší zahájení léčby jsou klíčovými prediktory návratu k výchozímu funkčnímu stavu po reperfuzi u pacientů s akutní iCMP s premorbidní disabilitou.

Introduction

The landmark randomized controlled trials established endovascular thrombectomy (EVT) as the standard of care for acute ischemic stroke (AIS) patients with large vessel occlusions [1]. More importantly, key trials informing current guidelines mainly included patients with little or no pre-stroke disability (modified Rankin Scale [mRS] score 0–1 or 0–2); therefore, the eligibility of patients with pre-existing neurological disability (mRS ≥ 3) remains uncertain. The fact that approximately one-third of patients with AIS present with a pre-stroke mRS ≥ 2 represents a substantial clinical challenge [2,3]. Excluding this substantial subgroup from potential therapeutic interventions has significant long-term implications for a large portion of the stroke population. In clinical practice, the use of EVT in patients with pre-stroke mRS ≥ 2 remains highly variable, with treatment decisions largely guided by individual clinician judgment. These decisions are shaped by healthcare and financial considerations (such as cost-effectiveness and perceived benefit), patient-related factors (including age, permanence of disability, and social background), and stroke-specific characteristics (e.g., stroke severity, infarct location) [4]. Although patients with pre-stroke disability were largely excluded from major EVT trials, intravenous thrombolysis (IVT) guidelines are relatively less restrictive. Thrombolysis may be considered in carefully selected patients with pre-stroke mRS ≥ 2, provided that the potential benefits outweigh the associated risks; however, it is applied considerably less frequently in this population compared to those with favorable pre-stroke functional status, similarly to current EVT practices [5].

In our study, we aimed to evaluate the efficacy of reperfusion therapies in a subpopulation of the Czech national registry for IVT and/or EVT comprising of patients with premorbid disability of mRS ≥ 3.

Methods

Details of the protocol have been published previously. In brief, the main study utilized data extracted from Czech national population-based databases: the Safe Implementation of Treatments in Stroke (SITS) and the Registry of Stroke Care Quality (RES-Q) registries [6]. Permission to analyze data from the registries was granted by the Ethics Committee of St. Anne's University Hospital, Brno, Czech Republic; individual patient consent was not required. The study protocol was also approved by the scientific committees of both registries.

Data extraction was performed from the registries between 2016 and 2020. Information was collected on baseline demographics; pre-stroke mRS score; vascular risk factors; admission blood pressure; pre-treatment glucose level; National Institutes of Health Stroke Scale (NIHSS) score; and IVT and EVT details. Stroke etiology was determined from the registry according to TOAST criteria [7]. Outpatient follow-up involved assessing the 3-month mRS score through an in-person visit with the patient, or alternatively, via a telephone interview with the patient, a family member, caregiver, or family physician.

The primary outcome was achieving a return to baseline functional status, defined as a ΔmRS of 0 at 3 months. Multivariate logistic regression was used to identify the predictors of this outcome.

Results

Of the 24,418 patients included in the registry between 2016 and 2020, premorbid

Tab. 1. Independent predictors of successful return to baseline functional status (ΔmRS = 0) in patients with premorbid disability after intravenous thrombolysis/EVT.

Predictor	Adjusted Odds Ratio (95% CI)	P-value
Demographics		
age (per year)	0.97 (0.95–0.98)	**< 0.001**
sex (female)	0.88 (0.71–1.09)	0.23
Clinical characteristics		
baseline NIHSS (per point)	0.94 (0.92–0.96)	**< 0.001**
pre-stroke mRS 3 (vs mRS 4–5)	1.42 (1.18–1.67)	**< 0.001**
Comorbidities		
hypertension	0.91 (0.73–1.12)	0.35
diabetes mellitus	0.86 (0.69–1.05)	0.14
atrial fibrillation*	0.78 (0.63–0.97)	0.03
heart failure	0.82 (0.64–1.04)	0.11
Treatment factors		
onset-to-treatment time (per minute)	0.99 (0.98–0.99)	**0.01**
EVT performed (vs. thrombolysis alone)	1.44 (1.17–1.76)	**< 0.001**
Stroke etiology		
atherothrombotic	1.69 (1.31–2.14)	**< 0.001**
cardioembolic	1.21 (0.95–1.53)	0.12
small vessel occlusion	1.14 (0.87–1.49)	0.33
other determined	1.28 (0.92–1.74)	0.14
undetermined	reference	–

Analysis based on post-hoc multivariate logistic regression of the Czech national registry for thrombolysis/EVT (2016–2020). Adjusted for age, sex, baseline NIHSS, prestroke mRS category, relevant comorbidities (hypertension, diabetes, atrial fibrillation, heart failure), treatment timing, treatment modality, and expected stroke etiology. Variable selection was based on clinical relevance and established prognostic factors. Bold values indicate statistical significance (P < 0.05).

*atrial fibrillation: OR < 1.0 indicates that absence of atrial fibrillation is associated with higher odds of successful return to baseline

CI – confidence interval; EVT – endovascular treatment; mRS – modified Rankin scale; NIHSS – National Institutes of Health Stroke Scale

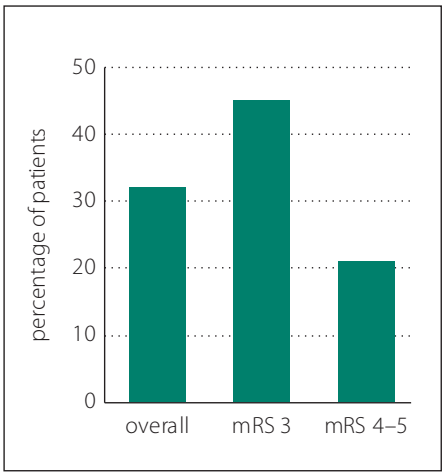

Fig. 1. Return to baseline functional status after reperfusion therapy in patients with premorbid disability.

mRS – modified Rankin scale

Obr. 1. Návrat k výchozímu funkčnímu stavu po reperfuzní léčbě u pacientů s premorbidní disabilitou.

mRS – modifikovaná Rankinova škála

mRS was available for 22,405 individuals, who comprised the main study cohort. Among them, 1,712 patients (7.6%) had premorbid disability (mRS ≥ 3) and received reperfusion therapy. The median age was 83 years (interquartile range [IQR] 75–88), and 1,004 (58.6%) were female. Most patients had moderate disability with pre-stroke mRS 3 (N = 1,204, 70.3%), while 429 (25.1%) had mRS 4, and 79 (4.6%) had mRS 5. The median baseline NIHSS score was 12 (IQR 7–18), indicating moderate-to-severe stroke severity. Cardiovascular comorbidities were common, including arterial hypertension in 1,467 patients (85.7%), diabetes mellitus in 710 (41.5%), atrial fibrillation in 453 (26.5%), and heart failure in 376 (22.0%).

Most patients received IVT (N = 1,658, 96.8%), while 172 (10.1%) underwent EVT, with 118 patients (6.9%) receiving both therapies. Of the 857 patients with available 3-month follow-up data, 275 (32.1%) successfully returned to their baseline functional status (ΔmRS = 0). Independent predictors of successful return included younger age (aOR 0.97 per year, 95% CI 0.95–0.98), lower baseline NIHSS (aOR 0.94 per point, 95% CI 0.92–0.96), absence of atrial fibrillation, and shorter onset-to-treatment time (aOR 0.99 per minute, 95% CI 0.98–0.99) (Tab. 1). Patients with premorbid mRS 3 were more likely to return to baseline than those with mRS 4–5 (aOR 1.42, 95% CI 1.18–1.67) (Fig. 1). The effect of reperfusion was more pronounced in patients with atherothrombotic stroke etiology (aOR 1.69, 95% CI 1.31–2.14) compared to cardioembolic etiology (aOR 1.21, 95% CI 0.95–1.53).

Discussion

Current guidelines for AIS recommend EVT for patients with a pre-stroke mRS score of 0–1 (or 0–2). Although patients with higher pre-stroke disability are not explicitly excluded from receiving IVT, it is administered significantly less often in this group. The evidence supporting reperfusion therapies for patients with higher degrees of disability is limited, as these individuals were not included in pivotal trials. A major concern is that, despite successful recanalization, pre-existing disability may limit meaningful functional recovery. However, approximately one-third of AIS patients present with premorbid disability, and systematically excluding them from reperfusion therapies could negatively affect outcomes in a substantial portion of the stroke population.

Our post-hoc analysis of the Czech national stroke registry included a cohort of 1,712 patients with pre-stroke disability defined as mRS ≥ 3. According to our results, approximately one-third of patients treated with IVT and/or EVT returned to their base-

line functional status, with this outcome being more pronounced in the mRS 3 group compared to the mRS 4 and 5 groups. The rates of return to baseline functional status in our cohort align with two recent meta-analyses that included studies involving patients with pre-stroke disability. One reported that EVT was associated with higher odds of returning to premorbid function (OR 2.37; 95% CI, 1.39–4.04), while the other found that IVT significantly increased the likelihood of functional recovery compared to no treatment (OR 7.26; 95% CI, 2.51–21.02) [8,9].

Our study adds to this literature by additionally exploring independent predictors of a favorable outcome among patients with pre-stroke disability. These included younger age, lower stroke severity, faster stroke care, and the absence of atrial fibrillation.

Future randomized controlled trials are needed to evaluate the safety and efficacy of reperfusion therapies in patients with pre-stroke disability. These studies should specifically focus on distinct patient subgroups. Patients with an mRS score of 2 are considered to have good functional status, being able to manage their own daily needs. Therefore, they should not be grouped with patients having mRS scores of ≥ 3. On the other hand, patients with an mRS score of 3 represent a crucial subgroup, as they are still capable of walking without assistance. Restoring functional status in these individuals remains an important goal. Furthermore, investigating patients with isolated cortical symptoms (e.g., aphasia) is crucial, as these symptoms indirectly affect functional status, making mRS scoring particularly challenging. Analyzing these subgroups could improve our understanding of the subtle effects of reperfusion therapies in patients with pre-stroke disability.

The significance of this issue continues to grow, as recent trials indicate that EVT may be beneficial even in patients with large acute ischemic lesions (ASPECTS 3–5), potentially without requiring advanced imaging and even within extended time windows [10,11]. This expansion in the pool of treatable patients presents a significant challenge for healthcare professionals, particularly when seeing patients with pre-stroke disability since we do not have RCT-derived evidence about reperfusion efficacy in this population even for conventional small-core, early-window settings.

In conclusion, one-third of patients in the national registry with premorbid mRS scores ≥ 3 returned to their baseline functional status after reperfusion therapy. Younger age, lower NIHSS, absence of atrial fibrillation, atherothrombotic etiology, and faster treatment are key predictors of this favorable outcome, which may aid clinical decision-making regarding IVT and EVT in this population.

Limitations

Our study has several important limitations. First, its retrospective, registry-based design inherently carries the risk of unmeasured confounding and selection bias. The mRS also has considerable subjectivity, particularly in the range of 1–3, where interrater variability is high and classification may be influenced by clinician judgment. As a result, some patients categorized as premorbid mRS 3 may in fact have had a milder degree of disability (mRS 1–2), potentially biasing our findings toward more favorable outcomes. Second, the study cohort represents a highly selected subgroup of patients with premorbid disability who were deemed eligible for IVT or EVT. In routine practice, patients with greater weakness, more severe comorbidities, or less favorable stroke characteristics are often excluded from reperfusion therapy for healthcare, financial, or prognostic reasons. Therefore, our sample likely underrepresents the full spectrum of premorbidly disabled patients, particularly those with more severe forms of disability (mRS 3–5), which limits the generalizability of our conclusions. Another important limitation is the lack of detailed subgroup analysis comparing patients with mRS 3 vs. mRS 4–5, despite evidence that these groups have different recovery potential. While our analysis showed that patients with premorbid mRS 3 were more likely to return to baseline than those with mRS 4-5 (aOR 1.42, 95% CI 1.18–1.67), a comprehensive comparison of treatment utilization patterns, workflow times, safety outcomes, and functional recovery trajectories between these subgroups would require adequate sample sizes and stratified analyses beyond the scope of the current study. This distinction is clinically meaningful, as patients with mRS 3 retain independent ambulation and may represent a fundamentally different population with distinct recovery potential compared to those with more severe baseline disability. Finally, as our analysis included only patients who received reperfusion therapy, it does not allow for direct comparison with untreated controls, and randomized controlled data are still needed to provide strict recommendations for clinical decision-making in this population.

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All other authors report no conflict of interest.

Ethics statement

The analyses presented in this study were conducted as part of a broader epidemiological research project focused on cerebrovascular events (stroke). This project was approved by the Ethics Committee of St. Anne's University Hospital in Brno on June 11, 2014, under approval number 36V/2014. The project involved a community-based epidemiological study and was designed in accordance with international ethical standards for epidemiological research. Data were obtained from the national Safe Implementation of Treatments in Stroke (SITS) and Registry of Stroke Care Quality (RES-Q) registries as part of routine clinical practice for monitoring the utilization and quality of stroke care. Given the retrospective nature of the study using anonymized registry data, individual patient consent was not required.

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