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Influence of including patients with pre-morbid disability in acute stroke trials: the HeadPoST experience

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Abstract

Background: Patients with pre-morbid functional impairment are generally excluded from acute stroke trials. We aimed to determine the impact of including such patients in the Head Positioning in acute Stroke Trial (HeadPoST) and early additional impairment on outcomes.

Methods: Post-hoc analyses of HeadPoST, an international, cluster crossover randomized trial of lying-flat versus sitting-up head positioning in acute stroke. Associations of early additional impairment, defined as change in modified Rankin scale (mRS) scores from pre-morbid levels (estimated at baseline) to Day 7 ('early ΔmRS'), and poor outcome (mRS score 3-6) at Day 90, were determined with generalized linear mixed model. Heterogeneity of the trial treatment effect was tested according to pre-morbid mRS scores 0-1 versus 2-5.

Results: Of 8,285 patients (38.9% female, mean age 68±13 years) with complete data, there were 1,984 (23.9%) with pre-morbid functional impairment (mRS 2-5). A significant linear association was evident for early ΔmRS and poor outcome (per 1-point increase in ΔmRS, adjusted odds ratio 1.20, 95% confidence interval 1.14-1.27; P <0.0001). Patients with greater pre-morbid functional impairment were less likely to develop additional impairment, but their risk of poor 90-day outcome significantly increased with increasing (worse) pre-morbid mRS scores (linear trend P<0.0001). There was no heterogeneity of the trial treatment effect by level of pre-morbid function.

Conclusions: Early post-stroke functional impairment that exceeded pre-morbid levels was associated with worse 90-day outcome, and this association increased with greater pre-morbid functional impairment. Yet, including premorbid impaired patients in the HeadPoST did not materially affect the subsequent treatment effect.

Clinical trial registration: HeadPoST is registered at http://www.ClinicalTrials.gov (NCT02162017).

Patients with pre-morbid functional impairment, quantified by estimated scores of 2-5 on the modified Rankin scale (mRS), are generally excluded from acute stroke trials when functional recovery is used as the primary endpoint, such as in evaluations of thrombolysis,[1, 2] mechanical thrombectomy,[3] and intensive blood pressure (BP) lowering.[4-6] Not only is this decision made from the viewpoint that such patients are considered less likely to benefit from acute interventions,[7] but also because of an effort to improve the precision in estimating the treatment effect using conventional dichotomous-based definitions of favorable outcome (e.g. mRS 0-1 or 0-2).[8] As a consequence, well highlighted in guidelines, there are deficiencies in the evidence-base supporting specific treatment recommendations in the 'real world', where patients with pre-morbid functional impairment are frequently encountered with acute stroke[9],[10] and who may benefit from avoiding adverse short-[11-15] and long-term[8] outcomes. The cluster crossover design of the international Head Positioning in acute Stroke Trial (HeadPoST) included patients with acute stroke and pre-morbid functional impairment through consecutive recruitment in order to reduce selection bias and optimize implementation of the head position interventions as part of routine practice. Herein, we report analyses to quantify the impact of including patients with pre-morbid functional impairment on the Day 90 functional outcome, specifically with regard to their potential to modify the randomized treatment effect in the trial. We also outline the different patterns ('trajectory') for recovery of function according to various grades of pre-morbid levels of function.

Methods

Design

HeadPoST was a large international, multicenter, cluster-randomized, crossover, prospective, open, blinded outcome evaluated, clinical trial conducted at 114 hospitals in nine countries.

The trial was designed to determine the comparative effectiveness of lying-flat and sitting-up head positioning (intervention), initiated soon after hospital admission in a broad range of patients with acute stroke, the full details of which are outlined elsewhere.[16, 17] Patients with a clinical diagnosis of acute ischemic stroke (AIS) or intracerebral hemorrhage (ICH) were consecutively recruited and assigned a head position according to the randomized cluster as soon as feasible after admission to hospital. Patients were encouraged to strictly maintain the randomized head position for 24 hours, but interruption was allowed for three non-consecutive periods (<30 minutes) for eating, drinking and toileting, should these not have been possible in the assigned position. HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

Procedures

Key demographic and clinical characteristics were recorded at the time of enrolment, including neurological severity measured using the National Institutes of Health Stroke Scale (NIHSS) at baseline, 24 hours, and Day 7 (or earlier, on discharge from hospital). Follow-up data were collected at Day 7 (or at hospital discharge if earlier), and at Days 28 and 90, unless death occurred earlier, by independent outcome assessors blind to group allocation. Data included final diagnosis, repeated NIHSS scores, and assessment of functional impairment using the mRS. Pre-morbid mRS was assessed retrospectively through self-report by patients or an appropriate surrogate.

Statistical analysis

As an initial testing found violation of the proportional odds assumption for using mRS as an ordinal outcome, the primary outcome for these analyses was ‘poor functional outcome’, defined by mRS scores 3-6 at Day 90 post-randomization. The term early post-stroke ‘additional impairment’ was calculated as the difference between the pre-morbid mRS

(estimated at baseline) and Day 7 (directly assessed; 'early ΔmRS' = Day 7 minus pre-morbid mRS scores), and evaluated as continuous and categorical measures.

Generalized linear mixed models with fixed intervention (lying-flat vs. sitting-up), and fixed period, random cluster, and random cluster-period effects were used to assess associations between early ΔmRS and 90-Day functional outcomes. The model was adjusted for unbalanced baseline characteristics/prognostic variables for outcomes that included country, age, sex, baseline NIHSS scores, time from symptom onset to commencement of the head positioning intervention, and history of stroke or atrial fibrillation (AF), current smoking status, stroke subtype, and prior use of antiplatelet and anticoagulant therapy. Sensitivity analysis included further adjustment for management factors over the first 7 days, including intensive care unit admission, acute stroke unit/ward admission, and receipt of subcutaneous unfractionated heparin, antibiotic treatment, intermittent pneumatic calf compression, and physiotherapy. To assess the interaction between baseline characteristics (including pre-morbid mRS) and association of early ΔmRS and outcome, interaction terms were added to the adjusted models. Heterogeneity of the treatment effect of lying-flat and sitting-up head positioning by pre-morbid mRS was also investigated. Data are presented with adjusted odds ratios (OR) and 95% confidence intervals (CI, and two-sided $P < 0.05$ were considered statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) was used for these analyses.

Latent class analysis (LCA) was used to differentiate patterns ('trajectories') of post-stroke recovery based on mRS scores obtained at baseline (ie pre-morbid estimates) and at Days 7 and 90. Using maximum likelihood estimation, the LCA computed the probability of each individual being assigned to a class to which they had the highest (posterior) probability of belonging,[18] and a final class was chosen to provide an optimal measure for meaningful interpretability and parsimony on Aikaike Information Classification (AIC) and Bayesian

Information Classification (BIC) indices.[18] Differences between trajectory classes were examined by chi-square and Kruskal-Wallis for categorical and continuous variables, respectively. LCA was performed with mRS as a continuous measure (ordinal analysis was not feasible) using the gsem in STATA Version 9.2 (Stata Corporation, College Station, TX). A Sankey diagram for each latent class allowed description of the pattern using R statistical package (version 2.15.0, R Foundation for Statistical Computing, Vienna, Austria).

Data sharing

Individual de-identified participant data used in these analyses can be shared by formal request with protocol from any qualified investigator to the Research Office of The George Institute for Global Health, Australia.

Results

Patient characteristics

Among the HeadPoST participants (11,093 patients, mean age 68 years, 39.9% female), 8,285 (74.7%) had complete mRS data (pre-morbid, and Days 7 and 90). The large sample size of the study led to significant differences across most baseline characteristics between included and excluded patients (Supplemental Table SI). Of the included patients with complete data (mean age 68 years, 38.9% female), there were 1,984 (23.9%) with pre-morbid functional impairment (estimated mRS scores 2-5), and the overall degree of early additional impairment defined by 'early ΔmRS' mean score was 0.89 (95%CI 0.86-0.91).

Table 1 shows that patients with greater early functional impairment (i.e. higher early ΔmRS scores) were older, more often female, had earlier commencement of the head positioning intervention, and higher baseline systolic BP, heart rate and neurological impairment. They were also less likely to have had a history of stroke and to have received prior antithrombotic treatment, but more likely to have AF.

Association of early ΔmRS with 90-Day functional outcome

Figure 1 shows the distribution of mRS scores, from pre-morbid estimates to Days 7 and 90. When analyzed as a continuous variable, every 1 point increase in early ΔmRS score was associated with a 20% increase in the odds of a poor outcome (OR 1.20, 95% CI 1.14-1.27; P <0.0001). The significant positive association persisted after further adjustment for management factors (OR 1.05, 95%CI 1.04-1.06; P <0.0001), and when early ΔmRS score was analyzed as a categorical variable: compared to the reference category (ΔmRS score ≤0), the OR (95%CI) across increasing ΔmRS scores were: 1 (0.97, 0.84-1.13); 2 (1.34, 1.14-1.58); and ≥3 (2.14, 1.76-2.60) (P for linear trend 0.025) (Supplemental Figure SI). Table 2 shows that the magnitude of additional functional impairment tended to decrease with each increase in mRS score of pre-morbid functional impairment, becoming negative with mRS scores >3: adjusted mean (95%CI) were 1.23 (1.20-1.26), 0.63 (0.58-0.69), 0.44 (0.36-0.53), 0.32 (0.23-0.42), -0.08 (-0.21-0.04) and -0.58 (-0.88 - -0.29) for mRS mean scores of 0 to 5, respectively.

Interaction between baseline characteristics and early ΔmRS score and outcome

Compared with patients with good pre-morbid function (mRS scores 0 or 1), those with pre-morbid functional impairment (mRS scores 2 to 5) were significantly older, more often female, and more likely to have a history of stroke, coronary artery disease, heart failure, hypertension, AF, diabetes mellitus, and antithrombotic use, and to present with greater neurological impairment (Supplemental Table SII). However, they were less likely to develop additional early functional impairment (ΔmRS ≥1) at Day 7 (Table 2). Although overall early ΔmRS mean scores were lower in patients with greater pre-morbid functional impairment, this score had prognostic significance (Table 2): OR (95%CI) for associations of early ΔmRS mean scores and Day 90 outcome were 1.70 (1.56-1.85), 1.79 (1.59-2.02), 1.86 (1.58-2.19), 2.25 (1.79-2.82), 2.43 (1.71-3.45), and 1.72 (0.86-3.47) for pre-morbid mRS

scores 0 to 5, respectively (P for linear trend <0.0001). The association was stronger for patients recruited in China (P for interaction 0.002) and in those who underwent reperfusion therapy (P for interaction 0.020), but was consistent across other patient subgroups defined by age, sex, NIHSS score, stroke subtype, AF, and prior use of antithrombotics (Table 2).

Effect modification of pre-morbid mRS score on treatment effect

There were no differences in the comparative effects of lying-flat and sitting-up head positioning by pre-morbid functional status (mRS scores 0-1, OR 1.08 [95%CI 0.97-1.21] vs. mRS scores 2-5 OR 1.04 [95%CI 0.87-1.23]) according to an ordinal shift analysis of the full range of mRS scores at Day 90 (P=0.671 for interaction) (Figure 1). The trial treatment effect did not change after excluding patients with pre-morbid functional impairment from analyses, nor was there any heterogeneity by level of pre-morbid functional impairment.

Among patients with AIS, reperfusion therapy was significantly associated with reduced risk of poor outcome at day 90 irrespective of premorbid mRS status (0.55 [0.43-0.70], and 0.62 [0.39-1.00] for premorbid mRS 0-1 and 2-5, respectively), though the association was stronger among patients with premorbid mRS 0-1 (P=0.030 for interaction).

Patient characteristics by four patterns of the recovery trajectory

The Sankey diagram (Figure 2) shows the temporal change in mRS scores (pre-morbid and Days 7 and 90). Table 3 outlines four patterns of recovery trajectory: to maintain stable good function (mRS mean [95%CI] scores of 0.21 [0.19-0.22], 0.76 [0.75-0.77], and 0.68 [0.66-0.70] at pre-morbid, and Days 7 and 90); to make some meaningful recovery (1.21 [1.20-1.23], 1.18 [1.16-1.20], and 0.95 [0.91-0.98]); to show decline (0.40 [0.37-0.43], 1.15 [1.12-1.72], 1.59 [1.58-1.61]); and to maintain disability (1.44 [1.43-1.45], 1.63 [1.62-1.65], 1.75 [1.74-1.77]). Most patients were classified as maintaining stable good functional status (62%); the proportion in other patterns were 13%, 15%, and 10%, for making some meaningful recovery, showing decline, and maintaining disability, respectively.

Supplemental Figure SII shows the temporal changes in mRS scores (pre-morbid, and Days 7 and 90) for each pattern.

Patients with persistent disability on follow-up had the worst baseline profile of pre-morbid function. Compared with those who showed functional decline, patients who made some meaningful recovery were younger, had less severe neurological impairment (lower NIHSS scores), but were more likely to have co-morbid cardiovascular risk factors and to have previously taken antithrombotics. Although they had a similar frequency of receiving intravenous alteplase, they were more likely to be admitted to ICU over the next 7 days compared to other patient groups.

Discussion

In this large international cohort, any deterioration in pre-morbid functional impairment experienced by patients within several days after the onset of acute stroke was associated with an increased risk of poor functional outcome at Day 90. Although this association was stronger in patients with greater pre-morbid functional impairment, who comprised approximately one quarter of the study population, their inclusion in the trial did not modify the comparative treatment effect of lying-flat versus sitting-up head positioning.
Interestingly, we found that patients who made some meaningful recovery within 90 days after symptom onset, compared with those who declined, were younger and milder baseline neurological impairment but had more comorbidities.

Our results confirm findings from several European studies that noted that patients with pre-morbid functional impairment had a higher burden of vascular risk factors, older age, and greater neurological impairment at the onset of acute stroke.[19, 20, 8] Moreover, data from 'real world' registries, such as the Safe Implementation of Thrombolysis in Stroke-monitoring study in Eastern Europe (SITS-EAST)[21, 20] and SITS–Monitoring Study (SITS-

MOST),[22] indicate that approximately 1 in 10 of all patients who receive intravenous alteplase (n=904) have pre-morbid impairment. These data also reflect the extrapolation of randomized evidence derived from otherwise healthy populations/people into clinical practice to frailer, disabled patients, who under-represented in acute stroke trials.

Despite strong evidence that intravenous alteplase improves the chances of recovery after AIS in a time dependent manner, irrespective of age or neurological severity,[23] there is uncertainty over the net balance of benefits over risks of this treatment in those with pre-existing functional impairment.[9],[10] Our analyses provide some justification for including these patients in research and practice. First, reperfusion therapy improved recovery at day 90 irrespective of pre-existing functional impairment, though the magnitude of the association was stronger among those with premorbid mRS 0-1. Second, we have shown that the degree of additional stroke-related functional impairment had a greater impact on long-term functional outcome in those with pre-morbid functional impairment compared to those without. Interventions with the potential to minimize additional functional impairment could translate into longer benefits in this group. Third, in AIS patients who receive reperfusion therapy, those with higher levels of early additional functional impairment have poor outcomes, but where the addition of functional impairment was associated with factors that reflect the underlying cause of stroke (age, sex, neurological severity, presence of AF), not the level of pre-morbid functional status. Finally, the inclusion of patients with pre-morbid functional impairment did not affect either the point estimate or precision of the treatment effect in the HeadPoST trial.

We found that patients who made some meaningful recovery were younger and had less severe initial neurological impairment despite a greater number of comorbid conditions compared with those who had shown decline. This is consistent with findings from literature, such as the study by Faircloth et al[24, 25] who identified three factors that might mitigate

against the disruptive impact of stroke: age, comorbidities and preexisting knowledge of stroke. In regard to the latter factor, the impact of the stroke may be lessened if the illness can be viewed as a natural part of growing older and where people are already managing existing comorbidities. We recognize, however, that our analyses were restricted to the physical and functional aspects of rehabilitation and that future studies are needed to understand the dynamic process of recovery that is shaped by the interaction of physical, emotional, and social domains.[26, 27]

A key strength of these analyses is their generalizability: despite being derived from a clinical trial of patients with acute stroke of predominantly mild to moderate neurological severity (median NIHSS score 4), the recruitment strategy was undertaken across a range of clinical settings to provide data on a broad range of stroke phenotypes. However, as in any observational study, there is the potential for confounding from incomplete adjustment, in particular those related to management confounders in the first 7 days, and recall bias from the assessment of pre-morbid mRS through self-report. In addition, there were 25% missing data which may also introduced bias as reflected in the proportion of patients with pre-morbid impairment (mRS 2-5) being lower in the excluded than included group.

In summary, any additional functional impairment experienced early after the onset of acute stroke was associated with worse Day-90 outcomes, and this association was stronger in patients with greater pre-existing functional impairment. Even so, patients with pre-morbid functional impairment may gain from treatments that limit further deterioration in function. Our analyses, therefore, provide some support for the enrolment of patients with pre-morbid disability into acute stroke trials.

Author contributions

XW and TM wrote the first draft of the report, XW and MO contributed to data analysis. LB, KS and CSA supervised the analyses. XW and CSA contributed to the concept and rationale for the study, and wrote the report. Others contributed to data collection and provided comments on data interpretation and the report.

Statement of ethics:

The appropriate ethics committee at each participating centre approved the study protocol. A senior executive officer at each centre acted as a 'guardian' and provided institutional consent for this low-risk intervention to be implemented as part of routine nursing care in each cluster. Written informed consent was sought from all patients or approved surrogates for ongoing assessments and data collection.

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These agencies had no role in the design of the trial protocol, in the collection, analysis, or interpretation of the trial data, or in the writing of the manuscript.

Disclosure

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References

1. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014 Nov 29;384(9958):1929-35.
2. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee T-H, et al. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. 2016;374(24):2313-23.
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016 Apr 23;387(10029):1723-31.
4. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008 May;7(5):391-9.
5. Delcourt C, Huang Y, Wang J, Heeley E, Lindley R, Stapf C, et al. The second (main) phase of an open, randomised, multicentre study to investigate the effectiveness of an intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT2). Int J Stroke. 2010 Apr;5(2):110-6.
6. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013 Jun 20;368(25):2355-65.
7. Ganesh A, Luengo-Fernandez R, Pendlebury ST, Rothwell PM. Long-Term Consequences of Worsened Poststroke Status in Patients With Premorbid Disability. 2018;49(10):2430-36.
8. Ganesh A, Luengo-Fernandez R, Pendlebury ST, Rothwell PM. Long-Term Consequences of Worsened Poststroke Status in Patients With Premorbid Disability. Stroke. 2018 Oct;49(10):2430-36.
9. Fiehler J, Cognard C, Gallitelli M, Jansen O, Kobayashi A, Mattle HP, et al. European Recommendations on Organisation of Interventional Care in Acute Stroke (EROICAS). Int J Stroke. 2016 Aug;11(6):701-16.
10. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018 Mar;49(3):e46-e110.
11. Kwok CS, Clark A, Ford GA, Durairaj R, Dixit AK, Davis J, et al. Association between prestroke disability and inpatient mortality and length of acute hospital stay after acute stroke. J Am Geriatr Soc. 2012 Apr;60(4):726-32.
12. O'Donnell MJ, Fang J, D'Uva C, Saposnik G, Gould L, McGrath E, et al. The PLAN score: a bedside prediction rule for death and severe disability following acute ischemic stroke. Arch Intern Med. 2012 Nov 12;172(20):1548-56.
13. Karlinski M, Kobayashi A, Czlonkowska A, Mikulik R, Vaclavik D, Brozman M, et al. Role of Preexisting Disability in Patients Treated With Intravenous Thrombolysis for Ischemic Stroke. 2014;45(3):770-75.
14. Abdul-Rahim AH, Quinn TJ, Alder S, Clark AB, Musgrave SD, Langhorne P, et al. Derivation and Validation of a Novel Prognostic Scale (Modified-Stroke Subtype, Oxfordshire Community Stroke Project Classification, Age, and Prestroke Modified Rankin) to Predict Early Mortality in Acute Stroke. Stroke. 2016 Jan;47(1):74-9.
15. Quinn TJ, Taylor-Rowan M, Coyte A, Clark AB, Musgrave SD, Metcalf AK, et al. Pre-Stroke Modified Rankin Scale: Evaluation of Validity, Prognostic Accuracy, and Association with Treatment. Front Neurol. 2017;8:275.

16. Munoz-Venturelli P, Arima H, Lavados P, Brunser A, Peng B, Cui L, et al. Head Position in Stroke Trial (HeadPoST)--sitting-up vs lying-flat positioning of patients with acute stroke: study protocol for a cluster randomised controlled trial. Trials. 2015 Jun 5;16:256.
17. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarria VV, et al. Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke. N Engl J Med. 2017 Jun 22;376(25):2437-47.
18. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. Prev Sci. 2013;14(2):157-68.
19. Foell RB, Silver B, Merino JG, Wong EH, Demaerschalk BM, Poncha F, et al. Effects of thrombolysis for acute stroke in patients with pre-existing disability. CMAJ. 2003 Aug 5;169(3):193-7.
20. Karlinski M, Kobayashi A, Czlonkowska A, Mikulik R, Vaclavik D, Brozman M, et al. Role of preexisting disability in patients treated with intravenous thrombolysis for ischemic stroke. Stroke. 2014 Mar;45(3):770-5.
21. Karlinski M, Kobayashi A, Mikulik R, Sanak D, Wahlgren N, Czlonkowska A, et al. Intravenous alteplase in ischemic stroke patients not fully adhering to the current drug license in Central and Eastern Europe. Int J Stroke. 2012 Dec;7(8):615-22.
22. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007 Jan 27;369(9558):275-82.
23. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet. 2014;384(9958):1929-35.
24. Furness PJ, Garrud P. Adaptation after facial surgery: using the diary as a research tool. Qualitative health research. 2010 Feb;20(2):262-72.
25. Hawkins RJ, Jowett A, Godfrey M, Mellish K, Young J, Farrin A, et al. Poststroke Trajectories: The Process of Recovery Over the Longer Term Following Stroke. Glob Qual Nurs Res. 2017 Jan-Dec;4:2333393617730209.
26. Dowswell G, Lawler J, Dowswell T, Young J, Forster A, Hearn J. Investigating recovery from stroke: a qualitative study. Journal of clinical nursing. 2000 Jul;9(4):507-15.
27. Kendall E, Catalano T, Kuipers P, Posner N, Buys N, Charker J. Recovery following stroke: the role of self-management education. Social science & medicine (1982). 2007 Feb;64(3):735-46.

Figure legend

Figure 1 Randomized treatment effect of lying-flat versus sitting-up head positioning on functional outcome according to mRS score at Day 90, by premorbid mRS score

Footnote: CI denotes confidence interval, OR odds ratio.

Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinical significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

Figure 2. Sankey diagram of the distribution of disability, pre-morbid and at Days 7 and 90,

on the modified Rankin scale (mRS)

Footnote: mRS denotes modified Rankin scale

Each color represents different mRS scores; the 3 horizontal positions indicate pre-morbid, and Days 7 and 90, time points; the vertical ordering shows mRS scores 0 to 6.

Changes of pre-morbid, and Days 7 and 90 mRS scores are shown in the table below:

Premorbid	mRS at Day 7 (%)							mRS at Day 90 (%)						
mRS (n, %)	0	1	2	3	4	5	6	0	1	2	3	4	5	6
0 (4690, 56.6)	27.4	35.7	23.2	13.7	-	-	-	24.7	44.7	10.1	12.4	4.4	2.3	1.5
1 (1611, 19.4)	11.1	48.0	18.6	11.3	11.1	-	-	18.0	40.7	8.8	15.9	7.9	4.6	4.2
2 (981, 11.8)	4.7	18.5	38.0	15.4	13.5	10.0	-	12.7	31.9	7.9	19.1	12.7	7.2	8.5
3 (620, 7.5)	0.8	5.7	14.8	37.9	21.9	17.6	1.3	3.9	21.6	5.5	22.4	15.2	12.6	18.9
4 (306, 3.7)	1.6	2.9	5.6	12.4	50.0	24.2	3.3	4.6	11.1	4.9	14.4	20.3	19.0	25.8
5 (77, 0.9)	3.9	2.6	2.6	3.9	15.6	68.8	2.6	1.3	3.9	3.9	15.6	16.9	28.6	29.9
Total	18.4	32.3	22.6	15.1	7.4	4.0	0.2	19.5	39.1	9.0	14.7	7.6	4.9	5.3