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# Validation of the simplified modified Rankin scale for stroke trials: Experience from the ENCHANTED alteplase-dose arm

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## Abstract

**Background and aims:** The structured, simplified modified Rankin scale questionnaire (smRSq) may increase reliability over the interrogative approach to scoring the modified Rankin scale (mRS) in acute stroke research and practice. During the conduct of the alteplase-dose arm of the international ENhanced Control of Hypertension ANd Thrombolysis StrokE stuDy (ENCHANTED), we had an opportunity to compare each of these approaches to outcome measurement.

**Methods:** Baseline demographic data were recorded together with the National Institutes of Health Stroke Scale (NIHSS). Follow-up measures obtained at 90 days included mRS, smRSq, and the 5-Dimension European Quality of life scale (EQ-5D). Agreements between smRSq and mRS were assessed with the Kappa statistic. Multiple logistic regression was used to identify baseline predictors of Day 90 smRSq and mRS scores. Treatment effects, based on Day 90 smRSq/mRS scores, were tested in logistic and ordinal logistic regression models.

**Results:** SmRSq and mRS scores had good agreement (weighted Kappa 0.79, 95% confidence interval (CI) 0.78–0.81), while variables of age, atrial fibrillation, diabetes mellitus, pre-morbid mRS (1 vs. 0), baseline NIHSS scores, and imaging signs of cerebral ischemia, similarly predicted their scores. Odds ratios for death or disability, and ordinal shift, 90-day mRS scores using smRSq were 1.05 (95% CI 0.91–1.20; one-sided $P = 0.23$ for non-inferiority) and 0.98 (95% CI 0.87–1.11; $P = 0.02$ for non-inferiority), similar to those using mRS.

**Conclusions:** This study demonstrates the utility of the smRSq in a large, ethnically diverse clinical trial population. Scoring of the smRSq shows adequate agreement with the standard mRS, thus confirming it is a reliable, valid, and useful alternative measure of functional status after acute ischemic stroke.

**Clinical Trial registration:** URL: http://www.clinicaltrials.gov. Unique identifier: NCT01422616.

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## Introduction and aims

The modified Rankin scale (mRS) is the most popular assessment tool for measuring the overall functional status in patients who have suffered a stroke or other form of neurological disability,[1] both in clinical practice and research.[2,3] However, due to criticism being raised over subjectivity in aspects of its categorization/scoring,[4] Bruno et al. developed the short, structured, simplified modified Rankin scale questionnaire (smRSq)[5,6] which has been shown to correlate with the size of the ischemic lesion,[6] health-related quality of life,[7] and neurological severity[8] in small single-center studies. The smRSq has also shown good reliability and validity in Chinese stroke patients.[9] However, it has not been validated in a broader population or in the context of international research where the modified Rankin scale (mRS) remains the gold standard method of outcome assessment. We aimed to compare scores on the mRS and smRSq, their predictor variables, their correlation with neurological impairment on the National Institutes of Health Stroke Scale (NIHSS) and health-related quality of life on the 5-Dimension European Quality of life scale (EQ-5D), and treatment effects using them as outcome measures, among participants of the alteplase-dose arm of the Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED).

## Methods

### Study design

ENCHANTED was an international, multicenter, quasi-factorial, prospective, randomized, open, blinded outcome assessed, clinical trial that assessed the effectiveness of low versus standard dose intravenous alteplase, and intensive versus guideline-recommended blood pressure (BP) management, in thrombolysis-eligible patients with acute ischemic stroke, the details of which are described elsewhere.[10,11] In brief, the first arm of the trial assessed 0.6 mg/kg compared to 0.9 mg/kg alteplase in 3310 patients (age $\geq$ 18 years) within 4.5 h of the onset of symptoms and followed up these patients to 90 days. The primary endpoint was death or disability defined by scores of 2 to 6 on the mRS. The trial was approved by the local ethics committees and regulatory bodies, and written informed consent was obtained from the patient or an appropriate surrogate. The trial is registered at ClinicalTrials.gov (NCT01422616).

### Measures

Demographics, clinical characteristics including the severity of neurological impairment on the NIHSS, were recorded in participants at the time of enrolment (baseline). The trial excluded patients with pre-morbid functional impairment (mRS scores > 1) but collected estimated pre-morbid mRS (0 or 1) for those included. Signs of cerebral ischemia on brain imaging, and any evidence of proximal vessel occlusion on computed tomographic angiography (CTA) or magnetic resonance angiography (MRA), were reported by clinicians. Assessors with a health professional background (doctors, nurses, or scientists) blind to treatment allocation and who had received in-person and online training (https://secure.trainingcampus.net) recorded mRS and smRSq scores by telephone or face-to-face interview in patients or a suitable proxy at 28 and 90 days post-randomization. These outcome assessors had no mandatory training in the use of smRSq. They were advised to first assess the patients with the mRS and then immediately administer the smRSq, as listed on the case report form. The seven-item mRS covers no symptoms (score 0), symptoms but no significant disability (1), slight disability (2), moderate disability (3), moderately severe disability (4), severe disability (5), and death (6). The smRSq takes on average 1.7 min to administer[7] and represents mRS items through yes/no answers to five questions addressing key functional states: living alone without any help from another person for bathing, toileting, shopping, preparing or getting meals, and managing finances; doing everything as before the stroke; being back to pre-stroke status; walking without help from another person; and being bedridden or needing constant supervision. The EQ-5D, which was also administered directly in a patient or proxy at 28 and 90 days, defines the state of general health across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels of responses within each dimension (no problems, some/moderate problems, and severe problems). The EQ-5D utility score integrates the ratings of the five dimensions into a single score, calculated using population-based preference weights for each subscale. The weights used in the present analyses were derived from a study based on a representative

sample of the UK population.[12] Utility scores express HRQoL quantitatively as a fraction of perfect health, with a score of 1 representing perfect health, a score of 0 representing death, and negative scores (minimum score −0.594) representing health states considered worse than death.[13]

### Statistical analysis

Strength of agreement on ordinal analysis[14] of the smRSq and mRS at Day 90 was assessed through Cohen's unweighted kappa (K) values of $\leq 0$ (poor), 0.01–0.20 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1 (almost perfect), and weighted kappa (Kw) values of $\leq 0.20$ (poor), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (good), and 0.81–1.00 (very good) agreement.[15] Multiple logistic regression was used to build prediction models for scores on the mRS and smRSq at Day 90 and to calculate C-indexes. Significant predictors ($P < 0.05$) from the univariate analyses were tested in multiple logistic regression models for their associations with outcomes. The non-significant covariates were removed until all the remaining predictors were statistically significant ($P < 0.05$). Collinearity between variables was checked. Baseline variables included in the models were: age (<65 vs. ≥ 65 years), sex, estimated prestroke function on mRS (0 vs. 1), baseline NIHSS score, history of atrial fibrillation (AF), diabetes mellitus, hypertension, previous stroke, coronary artery disease, and hypercholesterolemia, use of aspirin/other antiplatelet agent(s), and warfarin/other anticoagulation, and visible early ischemic change and proximal vessel occlusion on imaging. Correlations between smRSq and mRS at Day 90, and with NIHSS and EQ-5D utility scores at Day 90, were analyzed using Spearman correlation, with the r coefficient graded as 0.2–0.4 (weak), 0.4–0.7 (moderate), and 0.7–1.0 (strong). The treatment effects comparing low-dose alteplase to standard-dose alteplase in the trial were tested using scores derived from smRSq to compare with the study results generated using mRS. The non-inferiority margin was 1.14,[10,11] that is for the upper boundary of the 95% confidence interval (CI) for the odds ratio (OR) with low-dose alteplase as compared with standard-dose alteplase, of less than 1.14. Single logistic regression was used to test and estimate unadjusted OR of death and disability (mRS 2 to 6). Multiple logistic regression was used for adjusted OR in intention to treat and per protocol populations. For shift analyses of the smRSq scores, ordinal logistic regression was used. The variables adjusted in treatment effect analyses include site, time from symptom onset to randomization, score as a continuous measure on the NIHSS, age, sex, ethnicity, pre-morbid mRS score (0 or 1), pre-morbid use of aspirin, other antiplatelet agent or warfarin, and any history of stroke, coronary artery disease, diabetes mellitus, and AF. Testing was undertaken for the degree of agreement between smRSq and mRS at Day 28 using Kappa (K) and weighted Kappa (Kw), and for the strength of correlations between smRSq or mRS at Day 28, and NIHSS or EQ-5D utility scores at Day 28, using Spearman correlation with the r coefficient (Supplementary Appendix). P values $< 0.05$ were regarded as significant. SAS enterprise 7.1 was used in all analyses.

### Data sharing

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials. Individual participant data used in these analyses can be shared by request from any qualified investigators via the Research Office of The George Institute for Global Health, Australia.

## Results

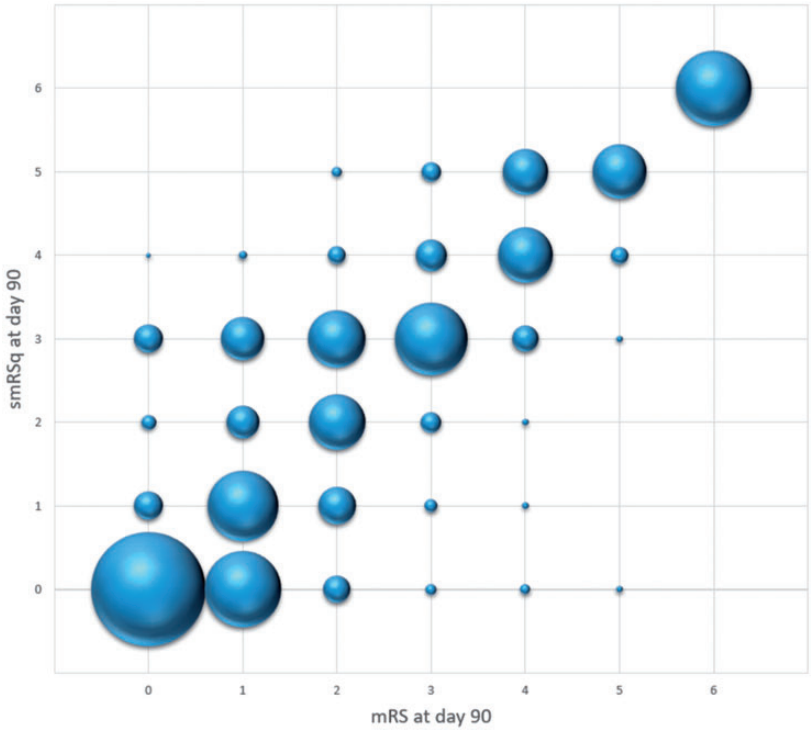
There were 3204 acute ischemic stroke patients with NIHSS scores recorded at baseline, and mRS, smRSq, and EQ-5D scores recorded at Day 90. Agreement between smRSq and mRS scores occurred in 2051 (64%) patients (Supplementary Table 1, Figure 1), and overall was moderate–good ($K = 0.57$, 95% CI 0.55–0.59, and $Kw = 0.79$, 95% CI 0.78–0.81).

Supplementary Table 2 shows the variables remained in the prediction models were common to both the smRSq and mRS at Day 90 after successively removing non-significant covariates; these included age (>65 years), AF, diabetes mellitus, pre-morbid symptoms, NIHSS scores, and signs of cerebral ischemia on imaging. C-indexes for the model fit were similar for the smRSq and mRS (0.74, 95% CI 0.72–0.76, and 0.75, 95% CI 0.73–0.77, mRS, respectively) (Figure 2).

Concordance was also evident for baseline NIHSS scores (positive correlation; $r = 0.442$, $P < 0.0001$ and $r = 0.455$, $P < 0.0001$, respectively) and EQ-5D utility score (negative correlation; r −0.836, $P < 0.0001$, and $r = -0.874$, $P < 0.0001$, respectively) and smRSq and mRS at Day 90.

Comparisons of the treatment effects using smRSq and mRS are presented in Supplementary Table 3. Both the dichotomous and ordinal outcomes using smRSq were similar to the outcomes from mRS. The unadjusted dichotomous outcome (score of smRSq 2 to 6), which was used to compare with the primary outcome of the alteplase-dose arm of the trial ($OR = 1.09$, 95% CI 0.95–1.25; one sided $P = 0.51$ for non-inferiority), occurred in 886 of 1609 patients (55.1%) in the low-dose group and in 863 of 1600 patients (53.9%) in the

**Figure 1.** Agreement between smRSq and mRS at Day 90. Area of bubbles represents the count at each score.




mRS: modified Rankin scale.

standard-dose group (OR 1.05, 95% CI 0.91–1.20; one-sided P=0.23 for non-inferiority). In the unadjusted shift analysis on smRSq scores comparing low-dose alteplase to standard-dose alteplase, the OR was 0.98 (95% CI 0.87–1.11; P=0.02 for non-inferiority) similar to that for mRS shift scores (OR = 1.0; 95% CI 0.89–1.13; P=0.04 for non-inferiority).

The results for agreement between smRSq and mRS at Day 28, and correlations with NIHSS and EQ-5D utility score at Day 28, are included in the supplementary appendix.

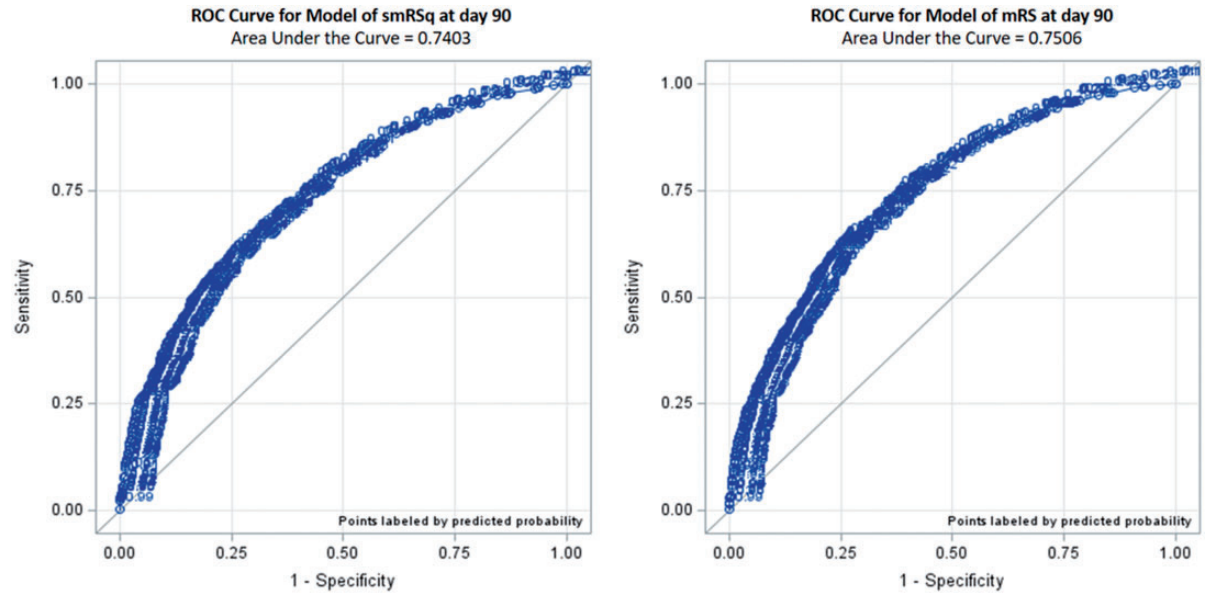
## Discussion

Our study validates the smRSq as a suitable stroke outcome measure by showing comparable scoring to the conventional mRS, similar level of moderate–strong correlations with the NIHSS and EQ-5D, common predictor variables, and similar treatment effects when used as trial outcome.

Dennis et al.[3] showed similar agreement between the mRS and smRSq using postal or telephone assessment in 225 participants, while Yuan et al.[9] found a higher degree of overall agreement than we have shown in their study of 150 Chinese patients. The factors identified in our predictive models for the smRSq and mRS support other outcome studies.[16,17] For example, in a multivariable analysis by Wahlgren et al.,[16] older age, high blood glucose, high NIHSS, and infarction on brain imaging were found to predict poor outcome (mortality or dependency) in patients treated with intravenous alteplase, while pre-stroke disability was only associated with mortality. Baseline severity, history of diabetes mellitus, ischemic stroke, and peripheral artery disease have also been reported to predict recovery after disabling ischemic stroke.[17] Katzan et al.[18] showed only a moderate correlation ($r = -0.53$, $P < 0.01$) between the mRS and EQ-5D utility score, possibly due to the greater number of patients with mRS scores of 0–2 (75%), which has shown a lower correlation with EQ-5D[19] than in the ENCHANTED[10] (~65%). Another study showed that the smRSq had moderate correlation with the physical ($r = 0.50$, $P = 0.005$) but only slight correlation with the mental components ($r = 0.36$, $P = 0.048$) of the 12-item short form questionnaire.[5]

More severe strokes (NIHSS scores > 10) are associated with higher mRS scores at hospital discharge.[20] NIHSS scores at Day 2 are a good predictor of mRS scores >3 at 90 days.[21] In a study of acute ischemic stroke patients treated with mechanical thrombectomy, NIHSS scores at baseline and hospital discharge were

**Figure 2.** ROC curves for the predictive models of mRS and smRSq at Day 90.




mRS: modified Rankin scale.

each significantly associated with 90-day mRS scores.[22] Another study has shown a similar moderate level of correlation between initial NIHSS and Day 90 smRSq scores ($r = 0.69$, $R^2 = 0.47$, $P < 0.001$)[5] to our study.

The smRSq appears easy to administer and automatically calculates a final score from the structured responses to five questions, whereas the mRS often requires the assessor to make a judgment call in deciding which category best fits a certain grading of disability or level of dependency. While training in the use of the mRS is often used to decrease error, this can be resource intensive for large studies. It is interesting to note that a high percentage of patients who scored 1 or 2 on the mRS scored 3 on smRSq in our study. One explanation could be that a high proportion of ENCHANTED patients experienced acalculia and difficulty managing finances without major motor disability after suffering a left middle cerebral artery stroke. This may have resulted in them answering negatively the first question of the smRSq, resulting in a score $\geq 3$. Another explanation is broader cognitive impairment but we did not collect such information in the study.

Our analyses found that similar factors were predictors of smRSq and mRS. This confirms the good correlation between the two scales and re-enforces that they are well-known predictors of poor outcome. Similarly, the correlation between smRSq and mRS is good which is not surprising as both scales correlated similarly with the NIHSS and EQ-5D.

In reviewing the treatment effects of the alteplase-dose arm of ENCHANTED, the use of the smRSq similarly failed to show that low-dose alteplase was non-inferior to standard-dose alteplase with respect to death or disability at Day 90, but was non-inferior with respect to ordinal shift of smRSq scores, which is consistent with those results using mRS.[10] This again reflects good correlation between the two measures, and for the smRSq to provide a comparable assessment of a treatment effect to that on the mRS.

Strengths of this study are the large database of prospectively and systematically assessed patients from a variety of countries and ethnic backgrounds. There are some limitations including that these were post-hoc analyses and that the same outcome assessors rated the mRS and smRSq. However, the Day 90 assessment case report form was structured for sequential recording of the mRS followed by smRSq, and these people were not provided with scoring answers to the smRSq questions. Another issue is that as patients with pre-morbid functional impairment/disability ($mRS > 1$) were excluded from the trial, we are unable to provide an assessment of any influence of this factor on the correlation between the measures. Moreover, the finding of large proportion of patients in the score of 3 using smRSq, similarly shown in the FOCUS trial,[23] suggests that distribution of patients across categories may differ between mRS and smRSq, which potentially influenced the results of this study. Finally, as this work pertains to a clinical trial involving acute ischemic stroke patients of predominantly mild–moderate severity, caution may be required in generalizing these results to a more severe patient population or in those with acute intracerebral hemorrhage.

In summary, our study has shown that the smRSq has comparable scoring and construct to the conventional mRS, and provides a useful, reliable, and valid outcome measure in the assessment of patients with acute ischemic stroke.

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## Author contributions

XC undertook analyses and wrote the first draft of the article; CD, JL, and CSA interpreted the data; other authors provided critical review; all authors contributed to drafting and take responsibility for the content and integrity of this article.

## Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Anderson reports receiving fees for serving on advisory boards from Amgen, Boehringer Ingelheim, and lecture fees and travel support from Takeda. Chalmers reports research grants and lecture fees from Servier for the ADVANCE trial and post-trial follow-up. Lavados reports receiving fees for serving on the advisory boards from ANGELS initiative and lectures fees from Boehringer Ingelheim and grant support from Bayer and Boehringer Ingelheim. The other authors report no conflicts of interest.

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## Supplemental material

Supplemental material for this article is available online.

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