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Editorial Review of Ganesh et al

Title: Lump or Split? Which version of the modified Rankin Scale should we use for stroke trials?

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Introduction

The modified Rankin Scale (mRS) is commonly used as a measure of global disability in stroke trials.[1,2] Its advantages include excellent construct validity and feasibility,[2] minimal time requirement, and flexibility for either face to face or telephone delivery.[3] However, disadvantages include low reliability (kappa=0.25,[4] and that the 7 point scale (0 to 6, with 6 being death) can miss important aspects of incremental recovery.[2] Although the mRS was originally developed as an ordinal scale, it has commonly been dichotomised for analysis, either 0-1 versus 2-6, or 0-2 versus 3-6. The clinical research community actively debates the best analytical approach to use in clinical stroke trials. Of note, in practice, the original mRS included both premorbid and post-morbid mRS assessments to allow meaningful comparative clinical interpretation. Although clinical trials often collect premorbid mRS as a core variable, interpretation as a pre-clinical assessment has been unclear, until now. Recently, Quinn and colleagues[5] conducted an evaluation of the pre-stroke mRS for its prognostic accuracy and validity as a measure of pre-stroke disability and reported it as a robust predictor of prognosis.[5]

Discussion

In this issue of Neurology, Ganesh et al[6] make a relevant and timely contribution to this statistical debate by comparing the performance of these 3 versions of the mRS at 3 months to objective criteria: 1 and 5 year mortality and morbidity, as well as health and social care costs. Importantly, they quantify what proportion of patients risk unnecessary exclusion from trials based on higher premorbid dichotomised mRS scales. Ganesh et al[6] test the validity of the different mRS representations for patients in the longer term recovery phases with different mRS grading, and suggest that it could help to inform better choices of primary outcomes. The authors use consecutive stroke patient data derived from the Oxford Vascular Study,[7] a well-established, population-based, prospective study with strong methodology, including standardised study coordinator training in the conduct of mRS assessment, physician ascribed case ascertainment, and meticulous follow up. We discuss three aspects of this rigorous, but complex analysis useful for interpretation of the results.

The most important consideration is circularity. The mRS scale includes a level for death and so when using the mRS to predict mortality at 1 and 5 years, we run into a self-fulfilling prophecy; the authors minimise this bias by excluding those who died by the 3 month mark. Likewise, the authors use mRS >1 or 2 to define morbidity, and so we have a similar circular argument when looking at mRS as a predictor of morbidity. The authors attempt to deal with this by eliminating those who had mRS >1 or 2 at baseline.

The next consideration is statistical overfitting. Intuitively, dichotomising the mRS ordinal scale would appear to result in loss of power and inversely, to fit a 6-level variable in the ordinal model would appear more powerful than fitting a 2 level variable in the dichotomised model. In essence, it is not a “fair” comparison, not “apples with apples.” The authors address this by using k-fold cross validation to calculate the predictive power of models; this method estimates the predictive power in a sub-sample and tests it on another subsample, and does this repeatedly to “shrink” the estimate of predictive power closer to the null to avoid overfitting or overly optimistic estimates of predictive ability.

The final aspect to review is predictive power, where the AUC represents the area under the ROC curve, which plots sensitivity vs. 1-specificity. The slope at any point on this curve represents the

positive likelihood ratio. In this paper's[6] 5-year mortality model, the AUC is explained as the likelihood that a randomly sampled stroke patient who died has a higher mRS score than a randomly sampled stroke case who survived. In predicting 5-year mortality, the base model with just age and sex has an AUC of 0.80. The ordinal mRS is a significantly although modestly better predictor than the dichotomised mRS for 5-year mortality. The AUC moves from 0.80 for the age and sex based model, to 0.82 for the 0-1 dichotomised mRS, to 0.83 for the 0-2 dichotomised mRS, to 0.84 for the ordinal mRS.

Overall, the results of this study provide additional support that mRS as an ordinal scale is preferable to a dichotomous approach. Premorbid mRS should ideally be included in clinical trial designs and trial data in order to increase representativeness of the sample and improve generalisability. The mRS, when analysed as an ordinal scale, provides the opportunity for clinicians to make a more meaningful clinical interpretation of the patient's recovery trajectory and see real improvement over time. Of note, age, female sex and social-economic deprivation independently predicted premorbid disability. Given that pre morbid disability has been associated with poor outcomes and is a robust predictor of prognosis,[5] clinicians can plan for additional short and long-term rehabilitation measures for older women living in social-economically deprived situations.

References

1. Fearon P, McArthur KS, Garrity K, Graham LJ, McGroarty G, Vincent S, et al. Prestroke modified rankin stroke scale has moderate interobserver reliability and validity in an acute stroke setting. *Stroke*. 2012;43:3184-3188
2. Taylor-Rowan M, Wilson A, Dawson J, Quinn TJ. Functional assessment for acute stroke trials: Properties, analysis, and application. *Front Neurol*. 2018;9:191
3. Wilson JT, Hareendran A, Grant M, Baird T, Schulz UG, Muir KW, et al. Improving the assessment of outcomes in stroke: Use of a structured interview to assign grades on the modified rankin scale. *Stroke*. 2002;33:2243-2246
4. Wilson JT, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. Reliability of the modified rankin scale across multiple raters: Benefits of a structured interview. *Stroke*. 2005;36:777-781
5. 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
6. Ganesh A, Luengo-Fernandez R, Wharton R, Rothwell PM, Study OV. Ordinal vs dichotomous analyses of modified rankin scale and 5-year outcome and cost of stroke. *Neurology*. 2018;XX-xx-xx.
7. Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (oxford vascular study). *Lancet*. 2005;366:1773-1783