The perfect stroke outcome scale remains the holy grail of our field—ever-elusive and sorely needed. Fifty years ago, Dr. John Rankin, working in a rehabilitation setting, devised a simple 6-point scale that made intuitive sense to all users; later, a category was added for death, resulting in a modified Rankin scale (mRS) as used today. Despite the simplicity and intuitive sense of the scale, the mRS was used little until it was rediscovered for many stroke therapy trials 15 years ago. Notably, the National Institute of Neurological Disorders and Stroke Tissue Plasminogen Activator for Acute Stroke trial used the mRS as 1 of 4 outcomes; the success of that trial catapulted the mRS to the forefront of stroke clinical trial design, and it has been ubiquitous ever since.

In approaching the mRS for use in the National Institute of Neurological Disorders and Stroke Tissue Plasminogen Activator for Acute Stroke study, my colleagues and I faced a thorny problem: how would we communicate the results of the trial to practicing doctors who had never heard of the scale? If we reported a numeric improvement in the scale, for example, of 1.4 points attributable to the treatment, what would that mean in clinical use? To solve the communication barrier, we decided to dichotomize the scale at 0 and 1 for a beneficial outcome. We reasoned that we could communicate the proportion of cures more easily to the general medical public this way. I called this the iceberg solution; if we moved the tip of the iceberg, we could infer that we had moved the entire iceberg. A statistically significant increase in the number of cures would be intuitively grasped, and in fact, that is exactly what happened. We left on the table, however, the remainder of the data at lower levels of the scale, and as it turned out, there was considerable clinical benefit to tissue-type plasminogen activator (tPA) hidden below the water line.

In the ensuing decades, there have been many attempts to analyze the mRS with more elegant and powerful techniques. We do not know whether any of these improved analysis techniques would be more useful than would the dichotomous approach, because no neuroprotectants have proven effective yet. When applied to our National Institute of Neurological Disorders and Stroke data set, it is clear that such newer analysis methods are more powerful. Statisticians and clinical trialists, however, argue continually over the applicability and suitability of these methods; especially troublesome are some of the assumptions required to apply the tests. Many of the more powerful methods do not lend themselves to easy communication, such as the iceberg solution.

To resolve some of these arguments, Howard and colleagues present a new way to analyze the Rankin scale based on the Mann-Whitney U test. Howard’s approach satisfies the burden of statistical rigor, yet retains a clinical flavor that is intuitive for the physician. No assumptions about the underlying data are needed, similar to any nonparametric statistical test. Computationally, the test is simple and can be adapted easily into any statistical software package; in a supplement, the authors graciously published their code, a real service to the community. The result addresses a simple clinical question, and the answer will be easily understood by the general medical readership.

The approach still contains some limitations, however, and clearly we do not yet have the holy grail in hand. Most importantly, the mRS itself is not ideal; additional research will be required to identify the ideal rating instrument. Another limitation is that Howard’s approach is not as transparent as it might seem at first glance. The devil lurking in the details concerns some of the statistical arcana, for example, the approach to handling tied scores (treated and placebo patients with the same score) with a permutation test. A final limitation is that Howard’s method does not add additional statistical power, compared with the currently used approaches. Given the currently prohibitive costs of clinical trials analyzed with traditional methods, one would hope that a novel analysis method would help reduce the numbers of patients required to find statistically significant results.

We all look forward to the day we find a neuroprotectant that benefits stroke patients. A side effect of that discovery will be the opportunity to test our known outcome scales, such as the mRS, and our analysis techniques, such as Howard’s test, to finally decipher the most effective and powerful approach.

Disclosures

None.

References


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The online version of this article, along with updated information and services, is located on the
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