Commentary: Disability Rating Scale in the First Few Weeks After a Severe Traumatic Brain Injury as a Predictor of 6-Month Functional Outcome

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In this issue of *Neurosurgery*, Yamal et al[1] explore the prognostic value of baseline characteristics plus the Disability Rating Scale (DRS) measured over weeks 1 to 4 after traumatic brain injury (TBI) for 6-mo outcome: a dichotomized classification as favorable vs unfavorable outcome according to the Glasgow Outcome Scale-Extended (GOS-E). The study is based on the dataset of the EPO-TBI (Erythropoietin in Traumatic Brain Injury) clinical trial on severe TBI that enrolled 200 patients.[2] The authors report high discriminative ability: an area under the curve (AUC) of 0.82 for baseline + DRS at week 1, increasing to 0.88 for baseline + DRS at week 4. They suggest that the 1- to 4-wk DRS is useful for clinical prognostication. Moreover, the DRS may be used as a surrogate endpoint for adaptive clinical trials. This is important not only because improving prognostication is relevant to practice and research, but also because availability of robust early surrogate endpoints would be a great asset to the design and conduct of clinical trials in severe TBI. There are two main issues to consider in interpreting the results.

First, statistical modeling issues play up. Dynamic prognostic modeling implies that new information (in this case the DRS) is added to a model based on baseline characteristics. Dropouts due to early death need to be accounted for. Indeed, the authors only considered data from patients who were alive at the time of prognostication when predicting favorable 6-mo outcome. This is a valid approach, but as a consequence, the number of patients included at the 4 time points (weeks 1-4) differs. Furthermore, the number of patients included in the development of the models was limited. The authors performed extensive validation procedures in random test parts of the data to prevent overoptimistic estimates of model performance. Obviously, external validation data are required to assess the generalizability of the findings.[3] It may not be surprising that adding new information as it becomes available over time increases the performance of a model. A basic question is if the DRS is the best summary measure to quantify this new information or that perhaps a constellation of clinical features might perform as well or even better. The DRS is not an interval scale and is not even ordinal. Hence, treating it as a continuous variable in analysis is debatable. The DRS consists of 4 components (arousal/awareness, cognitive ability to handle self-care functions, physical dependence, and psychosocial adaptability). The physical dependence component has similarities to the GOS-E, and, indeed, Figure 2[1] would appear to indicate that "level of functioning," as scored under Physical dependence of the DRS, is a main contributor to discrimination in the 4-wk model.

Second, in interpreting discriminatory performance, the "natural" trajectory of outcome over time should be considered. It is likely that some patients may have attained favorable outcome at 4 wk after injury (the time of final DRS assessment). Inclusion of these patients in the prediction will lead to an easy prediction of later performance. More in general, our knowledge of the outcome trajectory after TBI is limited, and this relative lack of knowledge affects the applicability of using early prognostic endpoints, for example, the DRS at 4 wk in an adaptive trial design. Conventional wisdom is that most improvement after TBI occurs in the first 6 mo after injury, and, hence, 6-mo outcome is often used as a primary endpoint in clinical trials. A novel therapy may perhaps not immediately improve outcome in the interventional arm of a clinical trial, but it may accelerate recovery. This would be equally relevant. There is also the moral debate if outcome assessment at 6 mo would be appropriate for all clinical trials on severe TBI. The RESCUEicp (Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure) study,[4] investigating the efficacy of decompressive craniectomy for refractory increase in intracranial pressure, showed a 9% increase in survival with severe

dependence at 6 mo, but by 12 mo, there were 13% more survivors in the treatment group who were at least independent at home. Thus, the benefit of treatment may only become evident later, and restricting an early prognostic endpoint to 6-mo outcome in a clinical trial may carry a risk of inappropriate decisions early-on in an adaptive design. Such risk will be context-dependent and is likely to be influenced by the initial severity of the patient population under study. We agree with the authors that early prognostic endpoints have their limitations. The search for mechanistic endpoints should continue.

In conclusion, the study by Yamal et al[1] is relevant and innovative but should be regarded more as hypothesis generating than as providing a clear direction on the way forward in clinical trials on severe TBI. In particular, it highlights the need for research on dynamic predictive modeling and for further studies to document and predict the recovery trajectory after TBI.

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