Bringing Statistics to the Clinic to Predict the Future: Nomograms for Psychiatric Outcomes of Epilepsy Surgery

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Predicting Mood Decline Following Temporal Lobe Epilepsy Surgery in Adults

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Objective: To develop a model to predict the probability of mood decline in adults following temporal lobe resection for the treatment of pharmacoresistant epilepsy. Methods: Variable selection was performed on 492 patients from the Cleveland Clinic using best subsets regression. After completing variable selection, a subset of variables was requested from 4 epilepsy surgery centers across North America (n = 100). All data were combined to develop a final model to predict postoperative mood decline (N = 592). Internal validation with bootstrap resampling was performed. A clinically significant increase in depressive symptoms was defined as a 15% increase in Beck Depression Inventory–Second Edition score and a postoperative raw score >11. Results: Fourteen percent of patients in the Cleveland Clinic cohort and 22% of patients in the external cohort experienced clinically significant increases in depressive symptoms following surgery. The final prediction model included six predictor variables: psychiatric history, resection side, relationship status, verbal fluency score, age at preoperative testing, and presence/absence of malformation of cortical development on magnetic resonance imaging. The model had an optimism-adjusted c-statistic of .70 and good calibration, with slight probability overestimation in higher risk patients. Significance: Clinicians can utilize our nomogram via a paper tool or online calculator to estimate the risk of postoperative mood decline for individual patients prior to temporal lobe epilepsy surgery.

Commentary

Although epilepsy surgery has been known to be superior to medical management for the treatment of drug-resistant temporal lobe epilepsy for 20 years,[1] it continues to be underutilized. At the core of this treatment gap is the limited ability to predict an *individual's* outcome after epilepsy surgery–even if 58 out of 100 patients with temporal lobe epilepsy become seizure free after surgery, how does this translate to an individual sitting in a clinic room, asking about the chances that *they* will live a better life if *they* choose to undergo surgery? Risk scoring systems can help bring data into personalized counseling. Nomograms are a risk assessment statistical tool that integrate multiple predictor variables to provide an individualized prediction of a particular outcome and have been increasingly used in epilepsy. Clinicians can now use a nomogram to help predict the chances of seizure freedom,[2] but also cognitive outcomes[3] and now, mood decline[4] after epilepsy surgery.

It is necessary to consider outcomes beyond seizure freedom when weighing various epilepsy treatments, from choosing an antiseizure medication to proceeding to epilepsy surgery.[5] Quality of life is only partially linked to seizure control among epilepsy patients, and cognitive and psychiatric comorbidities play an important role. Specifically, mood disorders have been an understudied but highly impactful comorbidity

relevant to epilepsy surgery outcomes. Prior studies have highlighted potential biological and psychosocial predictors of mood decline after epilepsy surgery,[6-8] but the ability to translate the complex interplay between these factors into a practical clinical tool for outcome prediction has been missing. Doherty et al[4] bridge this gap in their latest work.

In this multicenter North American study, nearly 600 patients from 5 North American sites (predominantly Cleveland Clinic) having undergone temporal lobe surgery were retrospectively analyzed. Clinically significant mood decline at a median time of 6 months from surgery was determined with a self-report measure of depressive symptoms (Beck Depression Inventory II), and defined in 3 ways, all of which had a high degree of concordance. Demographic, psychiatric, cognitive, surgical, and neurological predictors were collected based on the existing literature, and six easily identifiable variables spanning these 5 categories were included in the predictive model. Preoperative psychiatric history, dominant side of resection, relationship status (divorced), high preoperative verbal fluency score, younger age, and malformation of cortical development were all predictive of a higher probability of mood decline. Although 1 may hypothesize different mechanisms for how each of these variables contributes to postoperative depression and ways in which they may interact with 1 another, the model does not require an understanding of the interactions to accurately predict

the outcome. The final model displays good predictive accuracy, with a c-statistic of .70. The c-statistic identifies the proportion of patients in whom the predicted outcome matches the observed outcome–ie a c-statistic of .50 would indicate that the model performs no differently than chance.[9] Therefore, while a c-statistic of .70 is not perfect (which would be 1), it indicates that the model has a moderate ability to accurately predict mood decline. Not unexpectedly, mood decline was also correlated with adverse cognitive and seizure outcomes, although these were not included in the model, given that its main purpose will be in pre-operative counseling.

This tool is not ready to be used in every pre-operative counseling clinic session: it was developed in North American centers, in predominantly white and married patients, and only in those undergoing temporal lobectomy. The collaborating sites contributing smaller numbers of patients had younger and more ethnically diverse patients, who may fare differently after epilepsy surgery. In addition, extratemporal epilepsy surgery psychiatric outcomes differ in time course and severity.[8] Lastly, the outcome was considered in a cross-sectional manner, at a median time of 6 months from surgery, but a prior study showed that mood can change longitudinally after epilepsy surgery,[8] in a nonlinear manner.[10]

Still, this nomogram is a significant step forward and will help clinicians counsel individual patients on outcomes beyond that of seizure freedom when considering epilepsy surgery. One can also envision its use to identify high risk patients to design early diagnostic and therapeutic interventions after epilepsy surgery. Indeed, risk assessment tools are often used in general medical practice to guide intervention (eg the CHADS2 score can help stratify patients with atrial fibrillation to guide antiplatelet vs anticoagulation therapy). Similarly, patients identified as high risk for mood decline after epilepsy surgery may be targeted for screening and early intervention.

While the authors do not explicitly task themselves with elucidating mechanisms of mood decline after surgery, their nomogram may prove useful in the design of studies to understand the role of biological and psychosocial factors in the emergence of depression. Indeed, mood decline, in particular de novo depression, is a rare outcome of epilepsy surgery, making it hard to study longitudinally to identify predictive biomarkers. Being able to target an at-risk population more likely to develop the outcome of interest may enable adequately powered longitudinal studies designed to understand the causal relationship between biological and psychosocial factors and depression. Such studies may prove relevant not only to the field of epilepsy, but neuropsychiatry as a whole.

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