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Nomograms Should Not Be Used by General Neurologists When Considering Referral for Epilepsy Surgery

Development and Validation of the 5-SENSE Score to Predict Focality of the Seizure-Onset Zone as Assessed by Stereoelectroencephalography

Astner-Rohracher A, Zimmermann G, Avigdor T, Abdallah C, Barot N, Brázdil M, Doležalová I, Gotman J, Hall JA, Ikeda K, Kahane P, Kalss G, Kokkinos V, Leitinger M, Mindruta I, Minotti L, Mizera MM, Oane I, Richardson M, Schuele SU, Trinka E, Urban A, Whatley B, Dubeau F, Frauscher B. *JAMA Neurol*. 2022;79(1):70-79. doi:10.1001/jamaneurol.2021.4405

Importance: Stereoelectroencephalography (SEEG) has become the criterion standard in case of inconclusive noninvasive presurgical epilepsy workup. However, up to 40% of patients are subsequently not offered surgery because the seizure-onset zone is less focal than expected or cannot be identified. Objective: To predict focality of the seizure-onset zone in SEEG, the 5-point 5-SENSE score was developed and validated. Design, Setting, and Participants: This was a monocentric cohort study for score development followed by multicenter validation with patient selection intervals between February 2002 to October 2018 and May 2002 to December 2019. The minimum follow-up period was 1 year. Patients with drug-resistant epilepsy undergoing SEEG at the Montreal Neurological Institute were analyzed to identify a focal seizure-onset zone. Selection criteria were 2 or more seizures in electroencephalography and availability of complete neuropsychological and neuroimaging data sets. For validation, patients from 9 epilepsy centers meeting these criteria were included. Analysis took place between May and July 2021. Main Outcomes and Measures: Based on SEEG, patients were grouped as focal and nonfocal seizure-onset zone. Demographic, clinical, electroencephalography, neuroimaging, and neuropsychology data were analyzed, and a multiple logistic regression model for developing a score to predict SEEG focality was created and validated in an independent sample. Results: A total of 128 patients (57 women [44.5%]; median [range] age, 31 [13-58] years) were analyzed for score development and 207 patients (97 women [46.9%]; median [range] age, 32 [16-70] years) were analyzed for validation. The score comprised the following 5 predictive variables: focal lesion on structural magnetic resonance imaging, absence of bilateral independent spikes in scalp electroencephalography, localizing neuropsychological deficit, strongly localizing semiology, and regional ictal scalp electroencephalography onset. The 5-SENSE score had an optimal mean (SD) probability cutoff for identifying a focal seizure-onset zone of 37.6 (3.5). Area under the curve, specificity, and sensitivity were 0.83, 76.3% (95%CI, 66.7-85.8), and 83.3% (95%CI, 72.30-94.1), respectively. Validation showed 76.0% (95%CI, 67.5-84.0) specificity and 52.3% (95%CI, 43.0-61.5) sensitivity. Conclusion and Relevance: High specificity in score development and validation confirms that the 5-SENSE score predicts patients where SEEG is unlikely to identify a focal seizure-onset zone. It is a simple and useful tool for assisting clinicians to reduce unnecessary invasive diagnostic burden on patients and overutilization of limited health care resources.

Commentary

For patients with drug-resistant focal epilepsy, resective or ablative surgery can result in seizure control if the seizure-onset zone (SOZ) is identified and does not involve eloquent cortex. The decision to undergo surgery is complex and depends on multiple factors, including potential complications of the diagnostic and therapeutic interventions and postoperative seizure outcome. Some patients can show a mixture of favorable and unfavorable outcome prediction factors, such as concordant surface ictal electroencephalogram (EEG) abnormalities and neuropsychological deficits but without a lesion on magnetic resonance imaging (MRI). The presence of a SOZ inside an MRI-visible lesion does not necessarily correlate with surgical outcome and nonlesional epilepsy is not necessarily a negative prognostic factor for resective surgery.[1] Intracranial EEG (iEEG), with depth or subdural electrodes, is sometimes required to identify potential candidates.

Nomograms, statistical instruments that account for numerous variables to predict an outcome of interest for an individual patient, might help identify potential surgical candidates and ideally streamline the referral process to epilepsy centers where candidacy can be ascertained. Jehi et al[2] report on 2 nomograms to predict surgical outcome based on data collected from 846 patients before referral to their center. The results were validated with data collected from 604 patients from 4 additional epilepsy centers. Positive predictor factors included MRI findings, unifocal ictal onset, and age at time of surgery. While not exclusive to patients requiring iEEG, the authors conclude that these instruments were helpful in predicting favorable seizure outcome after surgery. It is not clear if these nomograms, and/or other prediction scales, have been validated in prospective cohorts and routinely used in general neurology clinics when considering referral to epilepsy centers.

In the current study by Astner-Rohracher et al,[3] the authors suggest a nomogram that can identify patients who might benefit from stereoelectroencephalography (SEEG). Using data from 128 consecutive patients, they identified factors that predicted focality on SEEG, which were seen in 37.5% of cases. SEEG electrode placement was tailored based on the electroclinical hypothesis, dividing patients into a focal (sublobar) or nonfocal (lobar, multilobar, multifocal, or missed) SOZ. For the ictal pattern analysis, the first 3 habitual electroclinical seizures were analyzed, determining the pattern's laterality and localization. Surgery was then performed in 83%, with 36% of patients with focal and 25% with nonfocal onsets achieving an Engel 1 outcome at 1 year of follow-up. This 5-point score was validated in a cohort of consecutive patients from 9 additional tertiary epilepsy centers, with each center contributing a minimum of 10 patients.

For statistical analysis, a stepwise approach was performed. An initial univariate analysis of potential predictors, with input from subject matter experts, was followed by logistic regression analysis and machine learning of the most influential variables. The final model considered a logistic regression model of 5 variables (a focal lesion on MRI, absence of bilateral independent spikes on scalp EEG, localizing neuropsychological deficit, strongly localizing semiology, and regional ictal scalp EEG onset) with discrimination assessed by calculating the area under the curve (AUC) and corresponding 85% confidence intervals, to create a score. Probability cutoff values were determined by bootstrapping. A range of useful cutoff values was then proposed for clinical practice. The score had an optimal mean probability cutoff for identifying a focal SOZ of 37.6 (standard deviation 3.5) with an AUC of 0.83, sensitivity 76.3%, and specificity of 83.3%; validation showed 76% specificity and 52.3% sensitivity. The authors conclude that this 5-point instrument is highly specific in predicting when will an SEEG be *unlikely* to identify a focal SOZ.

Strengths of the study include the large number of patients used in both the exploratory and validation cohorts and rigorous imaging and EEG data. On the other hand, there was a wide range of sensitivity observed among the centers used for validation, ranging from 27.3% to 87.8% and specificity between 56.2% to 100%. Additionally, information on the number of electrode contacts implanted per patient, which influences the ability to identify a SOZ, was not provided.

Using a similar stepwise approach to identify predictors of resective surgery and subsequent seizure freedom in patients studied with iEEG, Sivaraju et al[4] (*using data that predates my association with the Yale group*) report on a retrospective analysis of 178 consecutive patients who underwent iEEG followed by resection in 116 and with 5-year follow-up. Multivariable analysis identified variables, comparable to what Astner-Rohracher et al[3] report, as independent predictors of resection and absolute seizure freedom at 5-year follow-up. Importantly, some patients thought to have unfavorable predictors, such as nonlesional MRI, had a greater than 50% chance of seizure freedom if they underwent resection. My colleagues suggest that the presence of unfavorable predictors should not deter a presurgical evaluation, including with iEEG in selected patients.

Nomograms should not replace expert clinical judgment. There is concern that when used by general neurologists, referral of appropriate patients to epilepsy centers might be hindered.[5] As it is, epilepsy surgery is underutilized.[6] Furthermore, outcome scales can be helpful at the group level, but not necessarily for individual cases, given the degree of heterogeneity of the epilepsy population. The lack of identification of a SOZ does not rule out that a patient might not benefit from palliative therapies, such as neuromodulation, which are typically only offered at tertiary epilepsy centers and can greatly improve quality of life. Clinicians could benefit from collaborative multicenter prospective studies that determine what variables can best identify candidates that could benefit from an iEEG study, despite its potential complications and lack of ability to identify a unique SOZ.

David King-Stephens, MD
Department of Neurology
Yale School of Medicine

ORCID iD

David King-Stephens https://orcid.org/0000-0002-1455-9847

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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