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RESEARCH ARTICLE

Development of an online calculator for the prediction of seizure freedom following pediatric hemispherectomy using the Hemispherectomy Outcome Prediction Scale (HOPS)

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Abstract

Objectives: Although hemispheric surgeries are among the most effective procedures for drug-resistant epilepsy (DRE) in the pediatric population, there is a large variability in seizure outcomes at the group level. A recently developed HOPS score provides individualized estimation of likelihood of seizure freedom to complement clinical judgement. The objective of this study was to develop a freely accessible online calculator that accurately predicts the probability of seizure freedom for any patient at 1-, 2-, and 5-years post-hemispherectomy.

Methods: Retrospective data of all pediatric patients with DRE and seizure outcome data from the original Hemispherectomy Outcome Prediction Scale (HOPS) study were included. The primary outcome of interest was time-to-seizure recurrence. A multivariate Cox proportional-hazards regression model was developed to predict the likelihood of post-hemispheric surgery seizure freedom at three time points (1-, 2- and 5- years) based on a combination of variables identified by clinical judgment and inferential statistics predictive of the primary outcome. The final model from this study was encoded in a publicly accessible online calculator on the International Network for Epilepsy Surgery and Treatment (iNEST) website (https://hops-calculator.com/).

Results: The selected variables for inclusion in the final model included the five original HOPS variables (age at seizure onset, etiologic substrate, seizure semiology, prior non-hemispheric resective surgery, and contralateral fluorodeoxyglucose–positron emission tomography [FDG-PET] hypometabolism) and three additional variables (age at surgery, history of infantile spasms, and magnetic resonance imaging [MRI] lesion). Predictors of shorter time-to-seizure recurrence included younger age at seizure onset, prior resective surgery, generalized seizure semiology, FDG-PET hypometabolism contralateral to the side of surgery, contralateral MRI lesion, non-lesional MRI, non-stroke etiologies, and a history of infantile spasms. The area under the curve (AUC) of the final model was 73.0%.

Significance: Online calculators are useful, cost-free tools that can assist physicians in risk estimation and inform joint decision-making processes with patients and families, potentially leading to greater satisfaction. Although the HOPS data was validated in the original analysis, the authors encourage external validation of this new calculator.

KEYWORDS

hemispherectomy, hemispherotomy, online calculator, seizure outcomes

1 | INTRODUCTION

Cerebral hemispherectomy and its variants are among the most effective procedures for drug-resistant epilepsy (DRE) in the pediatric population.[1] On a group level, seizure freedom is achieved in a large proportion (~70%) of well-selected patients[1–6] with good long-term results.[2,3,5,7] However, the rate of seizure freedom following hemispherectomy is highly variable, ranging widely from 33% to 92% across institutions, patient populations, and studies.[2,8,9] Up to 30% of patients experience seizure recurrence, which is associated with reduced quality of life and a socioeconomic burden.[5] In addition, hemispheric surgery causes expected neurological deficits (e.g., hemiparesis and homonymous hemianopsia) and is associated with a non-negligible rate of surgical complications.[10,11] A subset of patients develop postoperative neurological complications despite an absence or limited improvement of seizure control or quality of life.[10,11] As such, determining

Key points

- The Hemispherectomy Outcome Prediction Scale (HOPS) Online Calculator predicts the probability of seizure freedom at 1-, 2- and 5-years post-hemispherectomy.
- The calculator output has an area under the curve (AUC) of 73.0% based on eight variables, including five from the original HOPS study.
- Online calculators are cost-free tools that can assist physicians in risk estimation and inform joint decision-making with families.

which patients will benefit from seizure freedom is imperative.[2] Any tool that can aid clinicians in selecting candidates, predicting outcome, and counseling parents is helpful in informing physician–parent/patient joint decision-making.

Ideal candidates for hemispheric surgery have DRE related to a hemispheric syndrome with contralateral neurological deficits[1,3,6,12,13] and have concordant presurgical test results[1,3,6] with expected postoperative stability or improvement of neurological impairment (e.g., language), cognition, and adaptive functioning.[14] Some studies have reported positive outcomes despite putative negative prognostic factors, such as bilateral electroencephalography (EEG) or magnetic resonance imaging (MRI) findings.[5,6,12,15,16] Overall, benefits of this surgery often outweigh the risks, even for non-ideal candidates.[4,6] The recently published Hemispherectomy Outcome Prediction Scale (HOPS) study identified five important independent predictors of post-hemispherectomy seizure freedom: age >3.5 years at seizure onset, absence of generalized seizure semiology, absence of contralateral hypometabolism on ^{18}fluorodeoxyglucose–positron emission tomography (FDG-PET), stroke as etiology of epilepsy, and absence of prior resective surgery.[1] These five variables were selected in the HOPS study for the purposes of developing an easy-to-use bedside seizure-outcome prediction score, at the cost of excluding several other variables that also influence seizure freedom.[1]

Online calculators have grown in popularity in neurosurgery in recent years, and have shown to be useful in predicting various outcome measures.[17–22] These online calculators lead to individualized risk estimation and improve patient-centered care by utilizing the patient's own parameters rather than statistical models.[18] Furthermore, these tools do not interfere with clinical workflows.[18] Online calculators place complex statistical models in the hands of physicians, with or without statistical knowledge, thereby increasing the likelihood of a meaningful clinical impact.[18]

The objective of this study was to develop a freely accessible, online tool that accurately predicts the probability of seizure freedom for any patient at 1-, 2-, and 5-years post-hemispheric surgery to provide clinicians with accessible and reliable prognostic information to complement their clinical judgment.

2 | METHODS

2.1 | Initial HOPS study

Consecutive patients with DRE at several participating centers across multiple continents who were younger than 19 years of age at the time of hemispherectomy, had at least one follow-up after the first postoperative week, and had seizure outcome data were included in the study.[1] Various surgical techniques resulting in a functional or anatomic disconnection/removal of the affected hemisphere were included, including anatomic hemispherectomies, hemidecortications, functional hemispherectomies, peri-insular hemispherotomies, trans-Sylvian hemispherotomies, and open or endoscopic-assisted parasagittal vertical hemispherotomies with the preoperative goal of seizure freedom.[1] In patients from whom more than one hemispheric resection was performed, data from the subsequent procedures were excluded.[1] Patients with a planned subtotal or palliative hemispherectomy were also excluded.[1]

Demographic, patient history, presurgical test results, and surgical variables were collected in the original study following a review of the literature and input from content experts, to develop the HOPS for prediction of post-surgical seizure freedom.[1] All contributing centers participated in accordance with local research ethics, and the organizing center received institutional review board approval for the study.[1]

2.2 | Predictors and model development

The two outcomes measured in the initial HOPS study were time-to-seizure recurrence (primary outcome) and Engel Class (I–IV).[1] However, the primary outcome of interest in this study was only time-to-seizure recurrence. Because HOPS was valiated in the original study,[1] re-validation was not performed, resulting in inclusion of all patients from the original study for development of the calculator. All statistical analyses and model creation were done in RStudio (Rstudio Inc., Version 1.2.1335).

Variables with >40% of data missing were eliminated. This was done to maximize the accuracy of multiple imputation by chained equations (MICE), which was performed to address missing data in the five HOPS variables.[23] Ten complete data sets were produced via MICE for model construction.[24] One hundred percent data completeness was achieved for all 14 variables. Variables that were removed included interictal/ictal EEG, single-photon emission computed tomography (SPECT), magnetoencephalography (MEG), and subtraction ictal SPECT coregistered to MRI (SISCOM) test results, as well as intelligence quotient (IQ) and behavior scores. The hemispherectomy approach was not included given that this is not an independent feature of epilepsy and is dependent on the individual skill and expertise of the surgeon. A detailed discussion to support this decision can be found

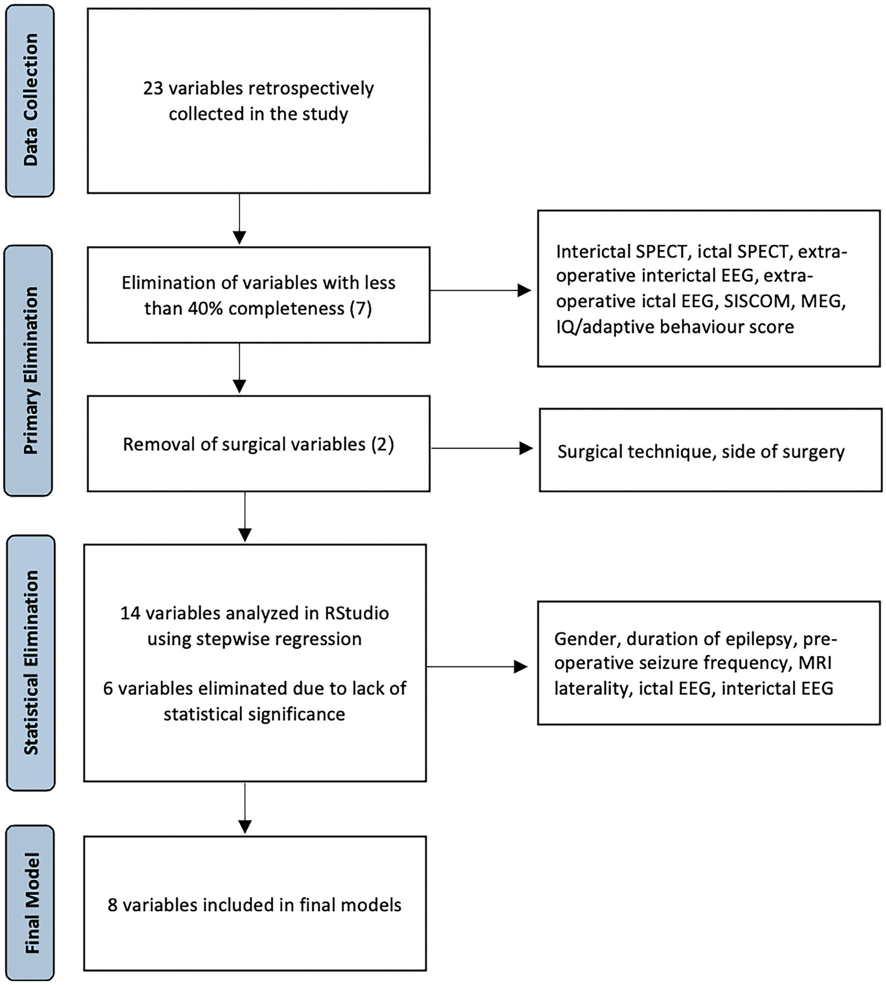

FIGURE 1 Flow diagram of variable selection process.

below. A variable elimination diagram is illustrated in Figure 1.

A multivariate Cox proportional hazards regression model was developed to predict the likelihood of seizure freedom at 1-, 2-, and 5-years post-hemispherectomy using the imputed data and based on a combination of clinical judgment and statistical analysis. Fourteen potential predictors were first analyzed via univariate Cox regression to identify putative predictors of seizure freedom. Variables with a *p*-value <.20 on univariate analysis underwent a bidirectional stepwise selection process according to the Akaike information criteria (AIC). Covariates that were selected for in a majority of the 10 imputed data sets were used to create a multivariate model for identifying independent predictors of seizure-freedom duration.[25] Regression coefficients and standard errors were combined and determined via Rubin's rule.[26] Hazard ratios (HRs), 95% confidence intervals (CIs), and *p*-values were obtained to characterize the relationships between the analyzed variables and time-to-seizure recurrence. The final included variables were evaluated by using the *riskRegression* package in R to generate receiver-operating characteristic (ROC) curves for the predicted risk of the training data from the 10 imputed multivariate models and compute the area under the ROC curve (AUC).[27] AUCs measure the performance of the predictive model, where 0.5–0.7 represents poor, 0.7–0.8 represents fair, and 0.8–1 represents excellent accuracy, respectively. The final model predicts the probability of seizure freedom at 1-, 2-, and 5-years post-hemispheric surgery for inputted data via the *predictSurvProb* function in the *pec R* package.[28] A two-sided *p*-value of <.05 was the threshold for statistical significance.

The HOPS data was validated in the construction of the clinical score[1] and therefore not revalidated in this study. This decision was made in order to include the maximum number of patients for development of the online calculator.

2.3 | Model presentation

The final model from this study was developed into a free, publicly accessible, online calculator that is displayed on the International Network for Epilepsy Surgery and Treatment (iNEST) website (https://hops-calculator.com/).

3 | RESULTS

For a detailed description of the sample population, please refer to the original HOPS article.[1] The variables that were selected for inclusion in the final model include the five original HOPS variables (age at seizure onset, etiologic substrate, seizure semiology, prior non-hemispheric resective surgery, and FDG-PET results) and 3 additional variables (age at surgery, history of infantile spasms, and MRI lesion). Hazard ratios, *p*-values, and 95% CIs for each variable used in the final model are reported in Table 1. Significant predictors of shorter time-to-seizure recurrence include younger age at seizure onset (HR = 1.13, 95% CI = 1.07–1.21, $p < .001$), older age at the time of surgery (HR = 1.02, 95% CI = 1.00–1.05, $p = .038$), FDG-PET hypometabolism contralateral to side of surgery (HR = 2.04, 95% CI = 1.26–3.28, $p = .004$), presence of contralateral MRI lesion (HR = 1.63, 95% CI = 1.19–2.24, $p = .004$), non-lesional MRI (HR = 2.12, 95% CI = 1.46–3.08, $p < .001$), non-stroke etiologies including hemimegaloencephaly (HR = 1.42, 95% CI = 1.07–1.89, $p = .017$), and Rasmussen's encephalitis (HR = 1.38, 95% CI = 1.01–1.90, $p = .045$). These variables were evaluated in each imputed data set via ROC and AUC metrics, which are shown in Figure 2. The average AUC for all imputed models was 72.0% ± 0.2% (0.72) with a range of 71.1–73.0% indicating fair accuracy.

TABLE 1 Variables included in the final Cox regression model.

Variable	HR	95% CI	*p*-value
Younger Age at Seizure Onset (years)[a]	1.13	1.07–1.21	<.001*
Older Age at Surgery (years)	1.02	1.00–1.05	.038*
Generalized Seizure Semiology[a]	1.13	0.88–1.44	.346
History of Infantile Spasms	1.27	0.99–1.61	.057
Prior Non-Hemispheric Resective Epilepsy Surgery[a]	1.36	1.01–1.83	.051
Etiology – PC/Stroke[a] (vs no PC/Stroke)	0.64	0.48–0.84	.002*
Etiology – RE (vs no RE)	1.38	1.01–1.90	.045*
Etiology – HME (vs no HME)	1.42	1.07–1.89	.017*
FDG-PET Imaging[a]			
Ipsilateral Hypometabolism Only	–	–	–
Contralateral Hypometabolism	2.04	1.26–3.28	.004*
Unknown	0.91	0.71-1.18	.478
MR Imaging			
Ipsilateral Lesion	–	–	–
Bilateral Lesions	1.63	1.19–2.24	.004*
Non-Lesional	2.12	1.46-3.08	<.001*

Abbreviations: HME, hemi-megalencephaly; PC, porencephalic stroke; RE, Rasmussen's encephalitis.
[a]Original HOPS variable.
*$p < .05$.

4 | DISCUSSION

The decision-making process to undergo hemispheric surgery for DRE requires accurate evidence-based estimation of risks and benefits within a framework that considers patient and caregiver-based values and preferences.[29] Online calculators are useful, cost-free tools that can assist physicians in risk-and-benefit estimations and inform joint decision-making with patients and/or guardians.[17,18,22,30–32] The format of an online calculator renders complex statistical models more accessible with the potential for broad clinical impact.[17,18,22,30–32] The HOPS calculator thus builds on the previously reported HOPS study, which identified five important predictors of post-hemispheric surgery seizure freedom (age greater than 3.5 years at seizure onset, absence of generalized seizure semiology, absence of contralateral FDG-PET hypometabolism, stroke-induced seizure etiology, and absence of prior resective neurosurgery) and developed an easy-to-use seizure outcome prediction score.[1] As a result, this online calculator renders the original prediction tool readily and widely used by clinicians to estimate the potential benefits of hemispheric surgery in a given patient into a

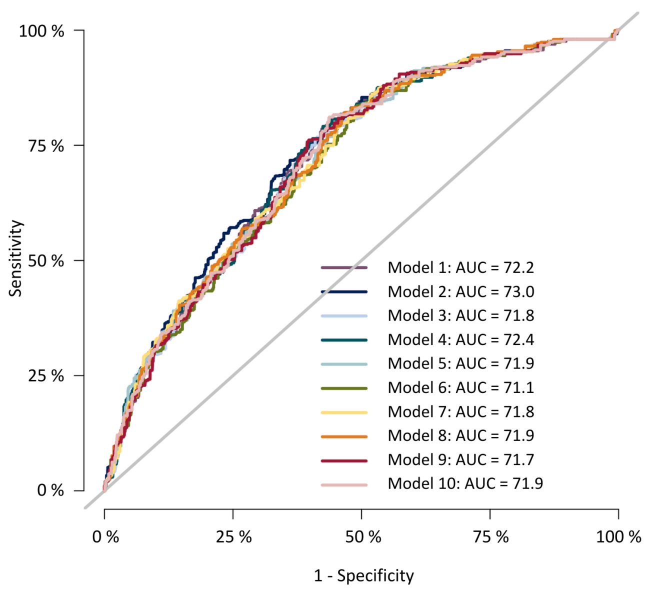

FIGURE 2 Receiver-operating characteristic (ROC) curve for Cox regression model used in the Hemispherectomy Outcome Prediction Scale (HOPS) calculator.

tool that epilepsy centers and families worldwide can access, utilize, and comprehend more easily.

The HOPS calculator provides additional benefits compared to the original scale, besides the increased accuracy. It is designed to perform projections at multiple time points (1, 2, and 5 years) rather than a single time point prediction, which better accounts for the time-dependent nature of seizure recurrence. The calculator also allows users to input more specific information than the scale (age as a continuous variable rather than 3 ranges, etiology subdivided into various categories rather than stroke vs non-stroke) and includes the "unknown" option for FDG-PET, which is less widely used in clinical practice, especially in the situation of a clear unilateral lesion. Although the scale is simple for epilepsy-specialized physicians, the calculator is more intuitive for other health care professionals such as primary care physicians and families. The calculator will help manage patient and family expectations through improved informed decision-making, potentially leading to greater satisfaction. Figure 3 depicts an example of the calculator used with sample data.

In addition to the 5 original HOPS variables, 3 additional variables (history of infantile spasms, MRI lesion, and age at time of surgery) were included in the HOPS calculator.[1] In order for such online calculators to provide accurate estimation of outcome, the variables included in the model should be validated by external datasets through other studies. A systematic review and meta-analysis by Hu et al. identified 1528 patients from 56 studies and reported similar predictors of seizure recurrence.[5]

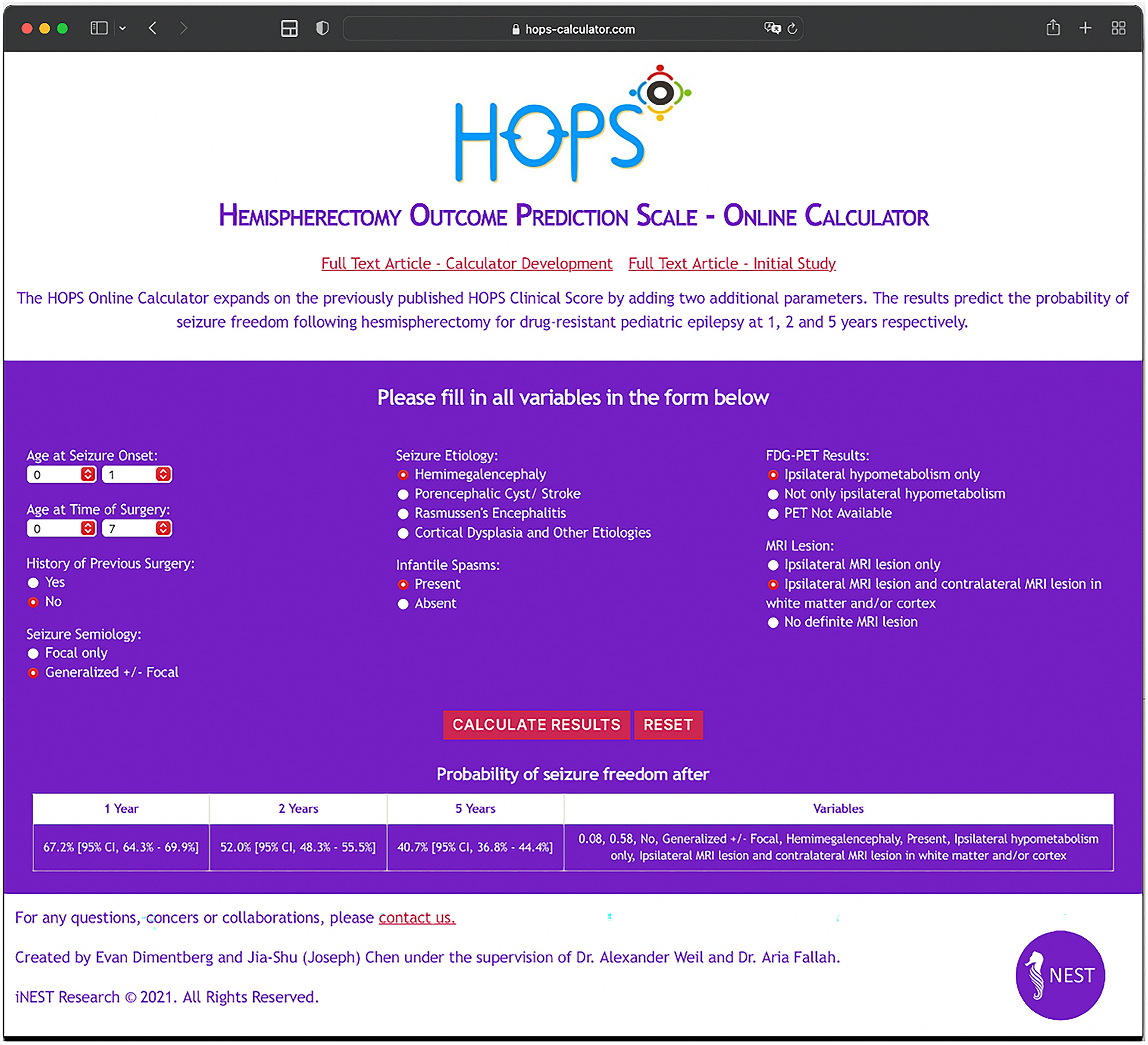

FIGURE 3 Application of the calculator on a sample patient.

Developmental etiologies, generalized semiology, and contralateral MRI lesions were all associated with poor prognosis, congruent with the results from the present analysis.[5] Hu et al. also indicated that the lack of contralateral interictal epileptiform activity was a significant predictor; however, this finding was not supported by the HOPS data.[5] Of all the significant predictors in the meta-analysis, interictal EEG was the least significant,[5] which may explain the discrepancy in results.

Contralateral MRI lesion was a significant independent variable associated with seizure recurrence and was added to the current model. There are conflicting findings in the literature regarding MRI abnormalities and their impact on seizure freedom following hemispherectomy. Some studies have found that bilateral (or contralateral) MRI abnormalities are associated with worse seizure outcome following hemispherectomy.[3,15,16,33,34] In a recent single center study of 69 patients undergoing hemispherectomy, Weil et al. found that the 21 patients (30.4%) who had contralateral MRI abnormalities had earlier time to seizure recurrence than patients with normal contralateral MRI.[35] In another study with similar findings, bilateral abnormalities on preoperative MRI were also associated with worse cognitive outcomes and neurocognitive development.[16] Conversely, some studies have shown that the presence of contralateral MRI abnormalities does not necessarily predict poor seizure outcome after hemispherectomy.[12,36–38] A single-center study of 110 children undergoing hemispherectomy found that the presence of contralateral MRI abnormalities (identified in 74%) was not associated with significant reduction in overall seizure outcome. However, contralateral MRI findings were only mild to moderate in most (85%) of these patients, included subcortical findings which are known to be less epileptogenic, and were always less prominent than the operated hemisphere. Furthermore, this study included nonvolumetric assessments of reduction in contralateral hemisphere volume and sulcal change, which are known to be very subtle, even in diseases like hemimegalencephaly.[16,39] In addition, when specifically evaluating for malformation of cortical developement and post-stroke etiology subgroups in this study, patients with contralateral abnormal cortical signal and thickness, respectively, had a higher likelihood of seizure recurrence.[36]

Although several earlier studies failed to identify an association between the type of hemispherectomy approach and postoperative seizure freedom,[2,4,5,12] a post hoc HOPS analysis revealed the superiority of vertical techniques compared to the lateral techniques for achieving durable seizure freedom.[40] Type of surgery was a significant predictor in the present analysis as well and the inclusion of surgical technique improved the concordance of the regression. However, surgical technique was excluded from the model given the interest in identifying only presurgical variables of interest. There are also inherent limitations in the data set, such as a disproportionately high number of patients who had undergone a lateral approach hemispheric surgery and lack of MRI-based data to evaluate completeness of disconnection, which preclude a definitive conclusion regarding the impact of surgical approach on outcome.[40]

Intuitively, surgeon and center experience should play an important role in outcomes following hemispheric surgery. However, the experience of a center, neurosurgeon, and neurology team is difficult to assess objectively. It is unclear whether the neurosurgeon's experience should be measured by frequency of hemispheric surgeries, total number of hemispheric surgeries, or total number of years in practice. Kurwale et al. performed a study that suggested 15–20 procedures are needed to achieve reasonable surgical skills in hemispherotomy.[41] A recent study found that increased years of surgeon experience was associated with a decreased likelihood of motor complications following peri-Sylvian/insular epilepsy surgery.[42] However, given the focus of the HOPS study, we did not explicitly collect data on surgeon experience and could not use the number of cases contributed by a center as a surrogate for surgeon experience. Turnover in personnel (neurology and/or neurosurgeon) is also a key factor to consider. Given the lack of objective data in assessing experience or any definitive literature suggesting its role in surgical outcomes, experience was not included in the study protocol. For maximal usability, the goal was to develop a preoperative predictive tool to determine seizure outcomes following surgery agnostic of the treating center or neurosurgeon.

It should be emphasized that the HOPS calculator predictions should not be used to reject any child from hemispheric surgery if the procedure is deemed clinically appropriate. Many children who are candidates for hemispheric surgery have severe epileptic encephalopathies and surgery that may not result in seizure freedom may still provide seizure and developmental benefit.

4.1 | Limitations

There are several inherent limitations to this study that were detailed previously in the original HOPS article.[1] These include (1) a selection bias, given that the current study includes only participants who were selected for resective epilepsy surgery based on a judgment that they are likely to have a successful outcome; (2) the exclusion of certain variables (e.g., surgical technique, EEG data) in the final model should not imply that those variables do not have prognostic value (surgical failures, for example, may be the result of incomplete disconnection as opposed to a true failure of the surgery; EEG data are intuitively an important part of the presurgical evaluation but were not included as part of this scale due to the high degree of missingness of data); (3) the use of multiple imputation to address missing data (to mitigate potential error, variables with less than 40% completion were excluded; FDG-PET was the only selected variable with more than 20% missing data); and (4) the retrospective nature of this study could lead to misclassification of preoperative variables given the multi-centric design and variability in interpretation (32 centers worldwide including multiple primary languages).

5 | CONCLUSION

In conclusion, the HOPS Online Calculator—designed to expand upon the published clinical score and increase its accessibility—predicts the probability of seizure freedom at various important timepoints with fair accuracy. The calculator includes all 5 variables from the initial study, with the addition of 3 additional predictor variables. Although the HOPS data were validated in the initial HOPS analysis, the authors encourage external validation using larger multicenter studies, which could this can also lead to future iterations of a hemispherectomy predictive score using additional variables.

AUTHOR CONTRIBUTIONS

Alexander G. Weil and Aria Fallah: Protocol design, study coordination, data collection, data analysis, manuscript drafting and review. Evan Dimentberg and Jia-Shu Chen: Data analysis, manuscript drafting. Chi-Hong Tseng: Data analysis, manuscript review and editing. Evan Lewis, George M. Ibrahim, Olivia Kola, Kao-Min Lin, Li-Xin Cai, Qing-Zhu Liu, Jiu-Luan Lin, Wen-Jing Zhou, Gary W. Mathern, Matthew D. Smyth, Brent R. O'Neill, Roy Dudley, John Ragheb, Sanjiv Bhatia, Daniel Delev, Georgia Ramantani, Josef Zentner, Anthony C. Wang, Christian Dorfer, Martha Feucht, Thomas Czech, Robert J. Bollo, Galymzhan Issabekov, Hongwei Zhu, Mary Connolly, Paul Steinbok, Jian-Guo Zhang, Kai Zhang, Eveline Teresa Hidalgo, Howard L. Weiner, Lily Wong-Kisiel, Samuel Lapalme-Remis, Manjari Tripathi, P. Sarat Chandra, Walter Hader, Feng-Peng Wang, Yi Yao, Pierre Olivier Champagne, Tristan Brunette-Clément, Qiang Guo, Shao-Chun Li, Marcelo Budke, Maria Angeles Pérez-Jiménez, Christian Raftopoulos, Patrice Finet, Pauline Michel, Karl Schaller, Martin N. Stienen, Valentina Baro, Christian Cantillano Malone, Juan Pociecha, Noelia Chamorro, Valeria L. Muro, Marec von Lehe, Silvia Vieker, Chima Oluigbo, William D. Gaillard, Mashael Al Khateeb, Faisal Al Otaibi, Niklaus Krayenbühl, Jeffrey Bolton, and Phillip L. Pearl: Data collection, manuscript review and editing.

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CONFLICT OF INTEREST STATEMENT

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