Is the crystal ball broken? Another external validation of the post-withdrawal seizure-relapse prediction model

We read with interest the work of Contento et al. They performed the third external validation of the Lamberink Prediction Model (LPM), which assesses seizure relapse risk following withdrawal of antiseizure medications (ASMs). In a first external validation, Lin et al. reported an area under the curve (AUC) of 0.71. They showed that the LPM outperformed predictions based upon the single largest randomized-controlled trial (RCT) to date, although somewhat overpredicted observed probabilities. Chu et al. provided a second Chinese cohort (AUC 0.61, again some overprediction). In contrast, Contento et al. concluded that model accuracy was inadequate because no single cutoff point provided high sensitivity and specificity (AUC ~0.5).

We agree that the LPM has limitations. Recruitment occurred mostly pre-2000 thus was lacking newer ASMs, genetics, and magnetic resonance imaging (MRI) studies. In contrast, in Contento et al. all patients underwent MRI, which could influence variables in the model such as electroencephalography (EEG) interpretation or focality explaining some divergence.

However, we have several concerns about their conclusions. First, the LPM was created from a large (N = 1769) diverse (N_countries = 7) data set, using “leave one out” internal-external cross-validation, which essentially performed 10 external validation steps in addition to the two from Lin et al. and Chu et al. We suggest caution before discounting the LPM in light of essentially only 1 of 13 validation steps suggesting poor performance. It would seem very surprising if the 12 variables contained in LPM (epileptiform EEG, number of seizures, duration seizure-free, and so on) predicted relapse no better than chance as the modified receiver-operating characteristic (ROC) curve of Contento et al. suggests. Moreover, validation is only as strong as the external data source. Selection mechanisms going from 4154 patients diagnosed with epilepsy down to just 205 (5%) who discontinued their ASM are not described, and another 36 of 205 were excluded due to missing data or incomplete follow-up. Including only 3% of those diagnosed with epilepsy raises concerns that the strong selection process determining discontinuation could explain divergence from the Chinese results.

Second, sensitivity and specificity are not the only metrics by which to judge a model. Observed vs predicted calibration may be a more intuitive way to assess model fit. In addition, the Discussion in the report of Contento et al. focuses on the inability of LPM to provide a single best cutoff. However, we believe that the predicted probability itself is the quantity of interest, rather than seeking an arbitrary dichotomous prediction. Even a perfectly accurate model could not inform what constitutes “high” vs “low,” which varies from patient to patient.

Third, Contento et al. interpreted the decision curve analysis of Lin et al. as showing usefulness only within limited ranges. However, that range (30%–65%) actually contains the majority of patients. It would be interesting if a future study compared the accuracy of clinician predictions vs the LPM, given it is generally the rule rather than the exception that big data-driven individualized prediction models outperform clinician intuition alone (a recent example).

Ultimately, showing predicted probabilities to patients influences decisions, and we acknowledge that the ability to predict outcomes is imperfect, encouraging future work. We appreciate the enthusiasm for critically appraising the best available science to move the field forward.

KEYWORDS
antiseizure medication withdrawal, epilepsy, predictive models

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CONFLICT OF INTEREST
The authors report no conflicts of interest. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS
All coauthors have been substantially involved in the study and the preparation of the manuscript. There are no undisclosed groups or persons who have had a primary role in the study and/or in manuscript preparation. All coauthors have seen and approved the submitted version of the paper and accept responsibility for its content.

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REFERENCES
Response: Brightening the crystal ball: A constructive reappraisal of the postwithdrawal seizure relapse prediction model

We are grateful to Terman and colleagues for their remarks about our paper on antiseizure medication (ASM) discontinuation and external validation of the Lamberink prediction model (LPM), recently published in this journal.\(^1\text{-}^3\)

Regarding the unsatisfactory performance of the LPM shown in our paper, this result is in part consistent with the work of Chu et al.,\(^4\) who also did not observe sufficient calibration of the model in predicting seizure recurrences at 2 years.

As for the patient population size (\(n = 133\)), although this is not a large sample, Lamberink et al. state that, in clinical practice, the LPM should be widely applicable even in small cohorts. Our study retrospectively included the 133 patients with sufficiently accurate clinical records of all the 205 patients with a diagnosis of epilepsy who discontinued ASMs at our epilepsy center within the time frame considered.

Regarding brain magnetic resonance imaging (MRI), it is true that almost all the patients underwent it. However, in our application of the LPM, none of the variables was influenced by the MRI results, as physicians based their diagnosis of seizure onset type on seizure semiology and electroencephalography.

As for the patient age, we agree that our results could be in part influenced by the features of our population, which included a larger proportion of adults than the other studies on LPM.\(^2\text{-}^4\text{,}^5\) However, in real life, it will be difficult to find two exactly matched populations.

As for ASM discontinuation, we agree that this decision should be taken together with the patient and that tools such as LPM might help. We believe, however, that many patients would be confused dealing with rough probability values, whose meaning would not be fully understood. Most of them would only accept a high probability of success, thus determining a low ASM discontinuation rate. Jacoby et al. showed that after counseling with the 1993 Medical Research Council model, the majority of patients actually avoided discontinuing ASMs.\(^6\text{-}^7\) In addition, it would be difficult for physicians to reach a decision when faced with probability values near .5. For all these reasons, we believe that the use of a dichotomous cutoff value would be more useful and easily applicable in clinical practice.

Regarding the issue of sensitivity and specificity, we agree that these could not be the only metrics in evaluating a prediction model, but it is difficult to expect a good fitting of a model if both measures do not simultaneously reach satisfactory levels. However, observed versus predicted calibration is certainly an alternative way to assess model fitting. Therefore, we again checked our results using the Hosmer–Lemeshow statistical test,\(^8\) which confirmed a low prediction accuracy of the LPM for seizure recurrence risk at 2 and 5 years (\(p = 0.01167\) and \(p = 9.22\times10^{-6}\), respectively).

In conclusion, we are glad that a discussion on the decision-making process of ASM discontinuation has been promoted by our paper. We believe that LPM needs further studies on its use in clinical practice, not for breaking but for making this crystal ball brighter.

**KEYWORDS**

AED withdrawal, antiseizure medications, epilepsy

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None.

**CONFLICT OF INTEREST**

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Vertical hemispherotomy for drug-resistant epilepsy: Toward confirmation of the HOPS study

To the Editors: We read with great interest the study reported by Aria Fallah et al. concerning the comparison of the real-world effectiveness of vertical versus lateral functional hemispherotomy techniques for pediatric drug-resistant epilepsy through a post hoc analysis of the HOPS study.1 We would first like to congratulate the authors for this remarkable study carried out using data from the HOPS study,2 a model of a constructive international collaboration that is particularly useful in the evaluation of techniques with rare and specific indications such as functional hemispherotomy. Through a methodologically rigorous analysis, the authors provide a strong argument in favor of better long-term effectiveness of the vertical hemispherotomy (seizure freedom = 85.5% at 10-year follow-up) compared to the peri-insular technique (seizure freedom = 57.2% at 10-year follow-up). This improves upon findings of a recent national multicenter study comparing these two techniques that could not demonstrate a statistical difference between them in terms of seizure outcomes.3 In this new analysis of the HOPS study, the difference between the two techniques is significant (log-rank test: \( p = 0.01 \)) and the observed effect is important (increased seizure recurrence odds: odds ratio = 3.67), which may have a direct impact on current clinical practice. One of the only limitations of this study is the asymmetry between the number of patients who underwent a lateral hemispherotomy, 600 from 21 centers, and those who had the vertical surgical approach, 72 from four centers. It is for this reason that we wish to share the preliminary results of our study on the effectiveness of our single-institution series, continuing the original work of Olivier Delalande on the vertical hemispherotomy,4 which includes 317 patients operated on with this technique. Seizure freedom was 78.3% (95% confidence interval = 72.6%-84.4%) at 10-year follow-up (see Figure 1). There was no significant difference with regard to the etiology of the epilepsy. The first point to emphasize is that our results are extremely close to those found in the 72 patients included in the HOPS study who underwent vertical hemispherotomy, which significantly strengthens the external validity of the study. A second point concerns the duration of the follow-up. Despite an exceptional number of patients (\( n = 672 \)) in the HOPS study, the 10-year follow-up is available in only 25 patients, including seven who had a vertical hemispherotomy. As the main conclusion of the study is a difference in maintaining long-term results, a criticism can be made about the small number of patients who had a long follow-up. Due to the longstanding use of this technique in our institution, 97 patients benefited from a 10-year follow-up. Our 10-year results are very close to those found in the HOPS study. That, once again, reinforces the conclusions made by the authors. Pending the proposal of a multicenter randomized study, we believe that the work of Aria Fallah et al. provides a strong argument for favoring a vertical approach in hemispherotomy.

**KEYWORDS**

disconnection, hemimegalencephaly, Rasmussen, Sturge–Weber

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**CONFLICT OF INTEREST**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE 1 (A) Kaplan–Meier curve depicting the seizure freedom function for the entire cohort of children undergoing vertical hemispherotomy at the Rothschild Foundation Hospital. (B) Comparison of Kaplan–Meier curves depicting the seizure freedom functions of the etiology. Log-rank analysis did not show any significant difference.
ANNOUNCEMENT

Epilepsia – December 2021 – Announcements

ILAE CONGRESSES

20–25 March 2022
3rd International Training Course on Neuropsychology in Epilepsy
Bordeaux, France
https://www.ilae.org/congresses/3rd-international-training-course-on-neuropsychology-in-epilepsy

10–13 April 2022
EEG in the First Year of Life – From Newborn to Toddler
Cambridge, UK & Virtual course
https://www.ilae.org/congresses/eeg-in-the-first-year-of-life1

9–13 July 2022
14th European Epilepsy Congress
Geneva, Switzerland
https://www.ilae.org/congresses/14th-european-epilepsy-congress

8–11 September 2022
11th Summer School for Neuropathology and Epilepsy Surgery (INES 2022)
Erlangen, Germany

WEBINARS

Canadian Epilepsy Teaching Network of the CLAE
The Canadian League Against Epilepsy is proud to launch the Canadian Epilepsy Teaching Network (CETN). We are excited to showcase monthly virtual rounds to be given by national and international experts in epilepsy. Sessions were designed based on the survey results conducted among the CLAE members and follow the ILAE competency-based curriculum. Sessions will be held Fridays, usually at 12 noon Eastern Time.
https://www.claegroup.org/CETN-Program

OTHER CONGRESSES

3–7 December 2021
AES Annual Meeting
Chicago, Illinois, USA & Virtual Meeting
https://www.aesnet.org/2021-annual-meeting

8–11 December 2021
European Congress of NeuroRehabilitation 2021 jointly with 27. Jahrestagung der Deutschen Gesellschaft für Neurorehabilitation
Virtual Congress
https://www.efnr-congress.org/

2022

24–28 January 2022
11th EPODES - Epilepsy Surgery – Basic
Brno, Czech Republic
http://www.ta-service.cz/epodes2021

27 February – 3 March 2022
American Society for Experimental Neurotherapeutics (ASENT) Annual Meeting 2022
Virtual meeting
https://asent.org/asent2022/

24–27 March 2022
16th World Congress on Controversies in Neurology
London, UK
https://cony2022.comtecmed.com/

3–8 April 2022
9th Eilat International Educational Course: Pharmacological Treatment of Epilepsy
Jerusalem, Israel
https://www.eilatedu.com/
8–10 April 2022
1er Curso Latinoamericano Teórico Práctico de Electroencefalografía Clínica
Santiago, Chile
https://www.clinicaepilepsia.cl/curso_electroencefalografia_clinica

26–28 April 2022
5th International Training Course on Neuroimaging of Epilepsy
Virtual course
https://www.mcgill.ca/neuro/international-training-course-neuroimaging-epilepsy-virtual

27–30 April 2022
60. Jahrestagung der Deutschen Gesellschaft für Epileptologie
Leipzig, Germany
https://www.epilepsie-tagung.de/

28 April – 2 May 2022
14th European Paediatric Neurology Society (EPNS) Congress: Precision in Child Neurology
Glasgow, UK & Virtual congress
https://epns-congress.com/

14–15 May 2022
ILAE British Branch Virtual 18th Specialist Registrar Epilepsy Teaching Weekend
Birmingham, UK
https://www.epilepsyteachingweekend.com/

22–25 May 2022
16th EILAT Conference on New Antiepileptic Drugs and Devices
Madrid, Spain
https://www.eilatxvi.com/

27–28 May 2022
Neurophysiology, neuropsychology, and epilepsy in 2022: Hills we have climbed and hills ahead
Honoring Professors Jean Gotman and Marilyn Jones-Gotman
Montreal, Canada

17–20 June 2022
10th Migrating Course on Epilepsy
Lviv, Ukraine
https://www.ilae.org/congresses/10th-migrating-course-on-epilepsy

25–28 June 2022
8th Congress of the European Academy of Neurology (EAN)
Vienna, Austria

16–23 July 2022
5th Dianalund Summer School on EEG and Epilepsy
Dianalund, Denmark
https://www.ilae.org/congresses/5th-dianalund-summer-school-on-ee and-epilepsy

18–29 July 2022
2022 Advanced San Servolo Epilepsy Course. Bridging Basic with Clinical Epileptology - 7: Accelerating Translation in Epilepsy Research
San Servolo (Venice), Italy
https://www.ilae.org/congresses/2022-advanced-san-servolo-epilepsy-course

2023

20–24 June 2023
15th European Paediatric Neurology Society Congress (EPNS): From genome and connectome to cure
Prague, Czech Republic
https://www.epns.info/epns-congress-2023/