University of Zurich[UZH]

Zurich Open Repository and Archive
University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2023

Predictive models for starting antiseizure medication withdrawal following epilepsy surgery in adults

Ferreira-Atuesta, Carolina ; de Tisi, Jane ; McEvoy, Andrew W ; Miserocchi, Anna ; et al ; Terziev, Robert ; Galovic, Marian

DOI: https://doi.org/10.1093/brain/awac437

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-229015
Journal Article
Accepted Version

The following work is licensed under a Creative Commons: Attribution 4.0 International (CC BY 4.0) License.

Originally published at:
Ferreira-Atuesta, Carolina; de Tisi, Jane; McEvoy, Andrew W; Miserocchi, Anna; et al; Terziev, Robert; Galovic, Marian (2023). Predictive models for starting antiseizure medication withdrawal following epilepsy surgery in adults. Brain: a journal of neurology, 146(6):2389-2398.
DOI: https://doi.org/10.1093/brain/awac437

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Predictive models for starting antiseizure medication withdrawal following epilepsy surgery in adults

Carolina Ferreira-Atuesta MD MSc[1,2], Jane de Tisi BA[1], Andrew W. McEvoy FRCS[1], Anna Miserocchi MD[1], Jean Khoury MD[3], Ruta Yardi MD[3], Deborah T. Vegh PhD[3], James Butler MD[4], Hamin J. Lee MD[4], Victoria Deli-Peri PhD[4], Yi Yao MD[5,6], Feng-Peng Wang MD[6], Xiao-Bin Zhang MD[6], Lubna Shakhatreh MBBS[7,8,9], Pakeeran Siriratnam MBBS, MPH[9], Andrew Neal MD,[7,8,9], Arjune Sen FRCP[10], Maggie Tristram[10], Elizabeth Varghese MD[11], Wendy Biney MD[11], William P Gray MD[12], Ana Rita Peralta MSc[13], Alexandre Rainha-Campos MD[13], António JC. Gonçalves-Ferreira PhD[22], José Pimentel PhD[13], Juan Fernando Arias MD[14], Samuel Terman M[25], Robert Terziev MD[15], Herm J. Lamberink PhD[16,21], Kees P.J. Braun PhD[20], Willem M Otte PhD[20], Fergus J. Rugg-Gunn FRCP[1], Walter Gonzalez MD[14], Carla Bentes PhD[13], Khalid Hamandi MD[12], Terence J. O' Brien MD[7,8], Piero Perucca PhD[7,8,9,17], Chen Yao PhD[18,19] , Richard J. Burman MD [4,10], Lara Jehi MHCDS[3], John S. Duncan FRCP[1,] , Josemir W Sander FRCP[1, 23,24,26], Matthias Koepp PhD[1], Marian Galovic PhD[1,15]

1. Dept of Clinical & Experimental Epilepsy (DCEE), NIHR University College London Hospitals Biomedical Research Centre, UCL Queen Square Institute of Neurology, London, WC1N 3BG & Chalfont Centre for Epilepsy, Chalfont St Peter SL9 0RJ, United Kingdom

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

2. Department of Neurology, The Icahn School of Medicine at Mount Sinai, New York, USA
3. Cleveland Clinic Epilepsy Center, Cleveland, USA
4. Constantiaberg Mediclinic Hospital, Division of Neurology, Neuroscience Institute, University of Cape Town, South Africa
5. Department of Epilepsy Surgery, Shenzhen Children's Hospital, Shenzhen, Guangdong, China
6. Department of Functional Neurosurgery, Xiamen Humanity Hospital, Xiamen, FuJian, China
7. Central Clinical School, Monash University, Level 6, 99 Commercial Road, Melbourne VIC 3000, Australia
8. Department of Neurology, The Royal Melbourne Hospital, Parkville, VIC 3050, Australia
9. Neurology Department, Alfred Health, Melbourne, VIC 3000, Australia
10. Oxford Epilepsy Research Group, NIHR Biomedical Research Centre, Nuffield Department of Clinical Neurosciences, University of Oxford, United Kingdom & Department of Neurology, 3rd Floor, West Wing, John Radcliffe Hospital, Oxford. OX3 9DU
11. Department of Neurology, University Hospital of Wales, Cardiff, CF144XW, UK
12. The Wales Epilepsy Unit, Department of Neurology, University Hospital of Wales & Division of Psychological Medicine and Clinical Neurosciences Cardiff, Cardiff University, Cardiff, CF144XW, UK

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

13. Centro de Referência para Epilepsias Refratárias (member of EpiCare). Hospital de Santa Maria - CHULN, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal
14. Epilepsy Center, Instituto Roosevelt, Bogota, Colombia
15. Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland
16. Department of Neurology, Haaglanden Medical Center, The Hague, The Netherlands
17. Department of Medicine, Austin Health, The University of Melbourne; Comprehensive Epilepsy Program, Austin Health, Heidelberg, VIC 3084, Australia.
18. Department of Neurosurgery, the First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, Shenzhen, Guangdong, China.
19. Shenzhen Epilepsy Center (Shenzhen Children's Hospital & Shenzhen Second People's Hospital), Shenzhen, China.
20. UMC Utrecht Brain Center, Department of Child Neurology, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands.
21. Department of Child Neurology, University Medical Center Utrecht, Utrecht, The Netherlands
22. Department of Neurosurgery, University Hospital Santa Maria, Lisbon, Portugal
23. Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, China
24. Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede 2103SW, Netherlands
25. University of Michigan Department of Neurology, Ann Arbor, MI 48109, USA
26. Department of Pediatric Neurology, Brain Center University Medical Center Utrecht, Utrecht, The Netherland

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

Correspondence:

Marian Galovic

Department of Neurology

University Hospital Zurich

Frauenklinikstrasse 26

8091 Zurich

Switzerland

Tel: +41 43 253 0648

marian.galovic@usz.ch

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Abstract

More than half of adults with epilepsy undergoing resective epilepsy surgery achieve long-term seizure freedom and might consider withdrawing antiseizure medications (ASMs). We aimed to identify predictors of seizure recurrence after starting postoperative ASM withdrawal and develop and validate predictive models.

We performed an international multicentre observational cohort study in nine tertiary epilepsy referral centres. We included 850 adults who started ASM withdrawal following resective epilepsy surgery and were free of seizures other than focal non-motor aware seizures (auras) before starting ASM withdrawal. We developed a model predicting recurrent seizures, other than auras, using Cox proportional hazards regression in a derivation cohort (n=231). Independent predictors of seizure recurrence, other than auras, following the start of ASM withdrawal were focal-aware seizures after surgery and before withdrawal (adjusted hazards ratio [aHR] 5.5, 95% confidence interval [CI] 2.7-11.1), history of focal to bilateral tonic-clonic seizures before surgery (aHR 1.6, 95% CI 0.9-2.8), time from surgery to the start of ASM withdrawal (aHR 0.9, 95% CI 0.8-0.9), and number of ASMs at time of surgery (aHR 1.2, 95% CI 0.9-1.6). Model discrimination showed a concordance statistic of 0.67 (95% CI 0.63-0.71) in the external validation cohorts (n=500). A secondary model predicting recurrence of any seizures (including auras) was developed and validated in a subgroup that did not have auras before withdrawal (n=639), showing a concordance statistic of 0.68 (95% CI 0.64-0.72). Calibration plots indicated high agreement of predicted and observed outcomes for both models.

We show that simple algorithms, available as graphical nomograms and online tools (predictepilepsy.github.io), can provide probabilities of seizure outcomes after starting

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

postoperative ASMs withdrawal. These multicentre-validated models may assist clinicians when discussing ASM withdrawal after surgery with their patients.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Running title: Withdrawal of Antiseizure Medication After Surgery

Keywords: epilepsy; epilepsy surgery; antiseizure medication; withdrawal; prognosis

Abbreviations:

ASM = AntiSeizure Medication

IQR = Interquartile Range

ILAE = the International League Against Epilepsy

HR = Hazard Ratio

aHR = Adjusted Hazard Ratio

MRI = Magnetic Resonance Imaging

EEG = Electroencephalogram

AIC = Akaike Information Criterion

FBTCS = Focal to Bilateral Tonic Clonic Seizures

WAMS = Withdrawal of Antiseizure Medication After Surgery

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Introduction

More than half of adults with drug-resistant epilepsy who undergo resective surgery achieve postoperative seizure freedom.[1] After successful surgery, they and their treating clinicians need to decide whether antiseizure medication (ASM) should be reduced or withdrawn. Continued administration of ASMs may have side effects, teratogenic implications and increase healthcare costs.[2] Conversely, ASM withdrawal might increase the risk of seizure relapse and subsequent injuries, epilepsy-related mortality, including SUDEP, occupational and driving constraints, and social stigma.[3,4] Several studies have identified risk factors for seizure recurrence following ASM withdrawal after epilepsy surgery. These include, among others, epilepsy duration at the time of surgery, characteristics of presurgical seizures, preoperative MRI abnormalities, the timing of ASM withdrawal, incomplete resection, and postoperative EEG abnormalities.[5–12]

Recent studies have shown the feasibility of predicting outcomes of ASM withdrawal in non-surgical cases,[13] and after paediatric epilepsy surgery.[11] A prognostic model synthesizing the clinical characteristics predicting recurrence after ASM withdrawal following successful epilepsy surgery in adults is not yet available.[14] The lack of tools to guide ASM withdrawal decisions leads to significant heterogeneity in the timing and strategies of drug discontinuation.[8,9,12,13,15,16] There is a need for practical instruments to support these clinical decisions and inform individuals and their relatives about realistic expectations of the risks and outcomes following ASM withdrawal.

We aimed to develop and validate a prediction model that provides probabilities of seizure recurrence following ASM withdrawal after epilepsy surgery in adults with readily available clinical variables.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Methods

We developed the prediction model using prospectively collected baseline and follow-up data from an ongoing consecutive registry of individuals who had epilepsy surgery at a tertiary centre in London (United Kingdom). The cohort has been reported previously in detail.[1] All participants were prospectively followed in yearly intervals (median total follow up duration 11 years, interquartile range [IQR] 6 – 16 years). Annual postsurgical seizure outcome was determined using the International League Against Epilepsy (ILAE) outcome scale,[17] and the participants' medication regime was noted. Data on ASM reductions' timing was corroborated by reviewing medical notes and extracting the exact timing of starting ASM withdrawal and seizure recurrences.

We randomly divided the London cohort into derivation and internal validation cohorts with a 2:1 ratio for model development and internal validation. For the development of the model, we only used the derivation cohort.[18]

For external model validation, we collected baseline and follow-up data of individuals undergoing epilepsy surgery with at least one year of postsurgical follow up at eight tertiary epilepsy referral centres (Cleveland [United States], Cape Town [South Africa], Shenzhen [China], Oxford [United Kingdom], Melbourne [Australia], Cardiff [United Kingdom], Lisbon [Portugal], and Bogotá [Colombia]). A detailed description of each cohort and the informed consent procedures are described in the Online Supplement.

In all cohorts, we included consecutive adults who underwent resective epilepsy surgery, had at least one year of postoperative follow-up, had no seizures other than focal non-motor aware seizures after surgery, i.e. ILAE outcome class 1 or 2,[17] and started reducing ASMs. We excluded those who did not achieve initial seizure freedom other than focal-aware

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

seizures (ILAE outcome class 3 or worse), did not attempt ASM withdrawal, had disconnective procedures, multiple brain surgeries, or had insufficient follow-up data. Acute postoperative seizures (i.e., occurring during the first 30 days after surgery) were not considered to be seizure recurrences.[19] Data for model development was complete.

Outcomes

The primary model outcome was time to seizure recurrence other than focal non-motor aware seizures (auras, i.e., ILAE outcome Class 3-6)[17] after the start of ASM withdrawal. Due to several considerations, we only considered seizures other than focal non-motor aware seizures, i.e. seizures with motor symptoms or those associated with impaired awareness. Firstly, the presence of focal non-motor aware seizures only may not be regarded as a poor outcome.[20] Seizures other than focal non-motor aware seizures are arguably clinically more relevant than focal non-motor aware seizures because they are more likely to cause injuries and lead to increased morbidity and mortality.[21] Secondly, individuals with only focal non-motor aware seizures may still consider ASM withdrawal and thus, including them makes the model more applicable.[22] Third, in some jurisdictions, focal non-motor aware seizures do not preclude driving.

On the other hand, given that focal non-motor aware seizures may have an impact on quality of life and represent a red flag for starting ASM discontinuation,[23] we developed a secondary model to predict any type of seizure recurrence (i.e., ILAE outcome Class 2-6) that included individuals that were completely seizure-free after surgery and before withdrawal (i.e. did not have any focal non-motor aware seizures).

As an additional outcome, we also assessed the time to complete withdrawal of all ASMs.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Development of the primary model

We performed a literature review of previously-reported predictors of seizure recurrence after ASM withdrawal following epilepsy surgery (see online Supplement). We chose predictors consistently reported to have a significant and independent association with the outcome and easily ascertained in different settings with varying clinical expertise. The selected predictors are also part of the routine diagnostic tests for people who ultimately undergo epilepsy surgery. We did not include data on postsurgical electroencephalography (EEG) because there were insufficient available data,[24] as this was not routinely performed in several centres involved in this study.[25] Data on percentage and rate of dose reduction, and reasons to halt withdrawal other than seizure relapse were not available.

Using Kaplan-Meier plots, we estimated the proportion of individuals remaining seizure-free at various time-points after ASM withdrawal commencement. We used univariable Cox proportional hazards regression analyses to assess the relevance of previously reported variables and identify any other potential predictors. Hazard ratios (HRs) were estimated with 95% confidence intervals (CI). The model was censored at the recurrence of a seizure other than focal non-motor aware seizures or on the last follow-up day.

Variables previously reported were included in the multivariable analyses and any significant variable ($p<0.05$) in the univariable analyses. The multivariable model was simplified by backward stepwise elimination based on the Akaike Information Criterion (AIC).[26] The AIC evaluates the fit of a model while penalizing overfitting and provides a means to select the most relevant variables regardless of their p-value. Lower AIC indicates a better fit, i.e., a higher likelihood with fewer parameters.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

We checked the statistical assumptions for Cox proportional hazard regressions and they were fulfilled.

Validation of the model

The performance of the model in the internal and external validation cohorts was assessed using discrimination and calibration.[27] Discrimination refers to how well the model distinguishes between participants with favorable or unfavorable outcomes. We used the concordance (c) statistic to measure discrimination, which corresponds to the area under the receiver operating characteristic (ROC) curve. Calibration indicates the agreement between outcomes that were predicted by the model and those that were observed. We used calibration curves, which plot the predicted risk given by the model against the observed risk, to assess calibration.

Prognostic models obtained from multivariable regression analyses can be overfitted and overestimate predictions when applied to a new cohort.[28] To get realistic precision estimates and confidence intervals, bootstrapping techniques were applied. A shrinkage factor was estimated from 1000 random samples to correct the c statistic for over-optimism, and 95% confidence intervals for risk estimates were generated to account for residual uncertainty. Internal-external cross-validation was performed to evaluate the model across different populations, as described previously.[18] The final AIC value was calculated over the pooled data set.[18]

Model predictions

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

The final risk estimates were estimated using combined data from all cohorts to increase generalisability.[18] To improve the practical usability of the model, we generated an easily estimated nomogram, a two-dimensional diagram that allows the graphical computation of a mathematical function. We also developed an interactive, user-friendly, and convenient web tool that provides individualized outcome estimates with corresponding 95% CIs and graphical representation.[29]

Secondary models

A secondary model was developed, including only those completely seizure-free after surgery (ILAE Class 1), i.e. those that did not have any postsurgical focal non-motor aware seizures. The secondary outcome parameter for these analyses was complete seizure-freedom, i.e. counting focal non-motor aware seizures as seizure relapses. As a sensitivity analysis, we also created a similar model that only included those undergoing temporal lobe surgery. We also developed a model of time to withdrawal of all ASMs in individuals that were completely seizure free after surgery. The same methodologies as described above were applied, and data was assessed and cross-validated in the combined cohort.

Development and validation of the presented models followed established recommendations (i.e. TRIPOD).[30] Two-sided p-values < 0.05 were considered statistically significant. Analyses were performed and updated using R version 3.6.2 using the packages "survival", “survminer,” “rms”, “survivalROC”.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Participant characteristics

The London cohort included 350 adults, of whom 231 randomly selected were used for model development (derivation cohort) and 119 for internal validation (internal validation cohort). External cohorts included 500 adults (Cleveland [*n*=98], Cape Town [n=105], Shenzhen [*n*=83], Melbourne [*n*=48], Cardiff [*n*=44], Lisbon [*n*=42], Oxford [*n*=40], Bogota [*n*=40]). We included 850 subjects overall, all of whom were seizure-free other than focal non-motor aware seizures between surgery and the start of ASM withdrawal (ILAE outcome 1 or 2, Supplementary Figure 1).

The overall clinical and demographic characteristics are provided in Supplementary Table 1. In the combined data set, the median time between surgery and the start of ASM withdrawal was 1.0 years (*IQR* 0.5-2.2). Kaplan Meier estimates indicate that 80% remained free from seizures other than focal non-motor aware seizures two years after starting ASM withdrawal and 72% after four years (Figure 1). At the end of follow-up, 317 (37%) participants had experienced a seizure relapse (including focal non-motor aware seizures), of whom 47 only had focal non-motor aware seizures. 308 (36%) individuals ultimately came off all ASMs. The median time between the start of ASM withdrawal to the complete withdrawal of all ASMs was 1.5 years (*IQR* 0.44-2.83).

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Primary model

Variables consistently described as relapse predictors (time between surgery and beginning of ASM withdrawal, history of FBTCS before surgery, number of ASMs at time of surgery, duration of epilepsy at time of surgery, hippocampal sclerosis on neuropathology, incomplete resection of an epileptogenic lesion, extratemporal lobe surgery, normal MRI before surgery, and presurgical seizure frequency) were included in the multivariable regression. The univariable analysis showed that postsurgical focal non-motor aware seizures before starting withdrawal were significantly associated with relapse after starting ASM withdrawal (Supplementary Table 2), and thus were also included.

After simplification based on the AIC, four predictors remained in the final multivariable model (Table 1A): focal non-motor aware seizures after surgery and before the starting ASM withdrawal, history of FBTCS, the time between surgery and starting withdrawal, and ASMs number at the time of surgery. Figure 1 displays the impact of these predictors on time to non-aura seizure relapse after starting ASM withdrawal in the combined data of all cohorts.

The model had an optimism-corrected *c* statistic of 0.68 (*95% CI* 0.58-0.79) in the internal validation (*n*=119) and 0.67 (*95% CI* 0.63-0.71) in the external validation (*n*=500) cohorts. Calibration plots indicated high agreement between predicted and observed data in the internal and external validation cohorts (Supplementary Figure 2). Internal-external cross-validation showed that the c statistic remained stable across different populations (Supplementary Table 3).

The model, named *WAMS* (Withdrawal of Antiseizure Medication After Surgery) was translated into an easy-to-use graphical nomogram (Figure 3A) predicting outcomes two and

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

four years after starting withdrawal. Time-variable prediction estimates can be estimated using a freely available practical online tool with a graphical user interface on https://predictepilepsy.github.io/

Secondary models

We performed a secondary analysis looking at predictors of complete seizure-freedom (binary outcome) in postoperatively seizure-free participants who did not have any focal non-motor aware seizures (ILAE Class 1, *n*=639). The resulting model (Figure 2, Supplementary Tables 4, 5) included the following predictors: history of FBTCS before surgery, presurgical seizure frequency, the time between surgery and starting withdrawal, duration of epilepsy before surgery and history of febrile seizure. The model showed an optimism-corrected *c* statistic of 0.68 (*95% CI* 0.64-0.72) and a high agreement between predicted and observed data (Supplementary Figure 2). Prediction estimates can be determined using a graphical nomogram (Figure 3B) or the online tool. The results for a similar model in people undergoing temporal lobe surgery can be found in the online supplement (Supplementary Tables 6, 7; Supplementary Figures 2, 3).

The results of a model predicting the withdrawal of all ASMs are displayed in the online supplement (Supplementary Tables 8, 9; Supplementary Figure 2). This model had an optimism-corrected *c* statistic of 0.73 (*95% CI* 0.68-0.78) and can be calculated using a graphical nomogram (Supplementary Figure 4).

ROC curves for all models are displayed in Supplementary Figure 5.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Case simulation

Examples of how to use the nomograms and online tools based on two fictional cases are illustrated in Figure 4.

Discussion

The decision to withdraw, or even just to reduce, ASMs after having reached seizure-freedom following epilepsy surgery is a common clinical problem. Here, we developed and validated predictive models that provide individualized probabilities of seizure outcomes in people that have started ASM withdrawal after epilepsy surgery. The models will provide objective recurrence expectations for people with epilepsy considering ASM withdrawal. They could assist presurgical counselling and decision making, especially in individuals who prioritize ASM withdrawal as a marker of surgical success. The models can be easily estimated using graphical nomograms or a freely available online tool.

The included predictors are clinically meaningful. We identified the timing of ASM withdrawal after surgery as a significant predictor in all models. This is relevant because the optimal time for starting ASM withdrawal after successful surgery is unknown, and approaches are heterogeneous, mainly relying on the clinician's personal experience and subjective risk assessment.[31–34] In the context of non-surgical individuals, a common practice is to consider ASM reduction after two years of seizure-freedom. Despite robust evidence, this approach is often implemented in postsurgical cases.[3,14,15,33] Some studies found that early withdrawal (<2 years) is associated with an increased risk of relapse compared with later withdrawal.[8,9,13,16,34] Others reported that early withdrawal did not affect long-term outcomes.[35,36]. Our models might support individualized decisions on the timing of ASM

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

withdrawal as we incorporated timing as an adjustable variable. The models will allow clinicians to adjust dynamically and individually postoperative observation time before attempting medication withdrawal according to individual characteristics and preferences. It might be feasible and safe to start withdrawal earlier in low-risk cases and prolong the observation period in high-risk individuals, although such an approach will require further prospective studies.

We found that focal non-motor aware seizures after surgery were the strongest predictor of seizure recurrence following ASM withdrawal. They may represent an early marker of surgical failure due to the incomplete removal of the epileptogenic zone.[1,37] It has been previously described that entirely seizure-free individuals had a lower risk of seizure relapse with impaired awareness in the following year than individuals with only focal non-motor aware seizures.[37]

Taking more ASMs at the time of surgery, having a higher preoperative seizure frequency, and preoperative FBTCS have been shown to be associated with epilepsy severity and increased risk of seizure relapse in surgical and non-surgical cases.[10,11,37] FBTCS involve and spread through distributed brain networks and maybe a biomarker of a more diffuse epileptogenic zone that is more difficult to completely resect.[38] Long presurgical duration of epilepsy[39]and having no history of febrile seizures[40] have previously been reported as risk factors for poor surgical outcome. These factors could account for a higher risk of seizure relapse when there is an attempt at ASM withdrawal. We found that acute post-surgical seizures, the resection location (temporal versus extratemporal), and the pathological findings were not associated with seizure freedom after starting postsurgical ASM withdrawal. These factors have, however, been previously related to surgical success.[41,42]

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

This study has several strengths. We evaluated data from one of the largest multicentre populations of people who attempted ASM withdrawal after successful surgery. When validated across nine cohorts from high and low-income countries, the models showed robust performance, supporting their generalizability.[27] Our models were well calibrated and may, thus, provide realistic statistical estimates of the risk of seizure relapse in individuals that have decided to attempt ASM withdrawal, which is relevant for decision making and follow-up recommendations.[27,29,43]

Data were acquired in the clinical setting of tertiary epilepsy referral centres. Thus, the findings reflect real-life scenarios, and the results can be readily applied to clinical situations. The models were developed using consecutive long-term single-center data from 1990-2016, but the external validation was done in several cohorts with recent data, contributing to temporal validation.[27] This confirmed the performance of the model in more contemporary settings given changes to the surgical candidates and procedures over the last decades. We conducted a review to identify predictors of outcomes comprehensively evaluated in previous reports. The selected predictors were well defined, easily measured, and routinely available. Additional models predicting complete seizure freedom and the likelihood of achieving complete ASM withdrawal were also developed. We implemented the main models in an online tool that will increase their accessibility and practicality.

Our study was devised in an intention-to-treat manner. We included all participants that decided to start ASM withdrawal, regardless of whether the withdrawal was completed or not. Thus, the models provide the probabilities of seizure recurrence to individuals that are considering to start ASM withdrawal, rather than to those who already successfully reduced

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

doses and are coming off all medications. The participants included in our study had a low pre-test likelihood of recurrence based on clinical expertise.

Developing a predictive model involves making compromises. We did not include predictors not routinely assessed in clinical practice or those that did not support sufficient validation data. Future studies might refine predictions by including data from postsurgical EEG, blood biomarkers, advanced neuroimaging, and genetic data. Such additional biomarkers could further improve model discrimination.

Our study has several limitations. Our results are only applicable to adults, and different models should be used for children.[11] The models should only be applied when data for each included predictor is available. Due to the cohorts' observational character, we could not implement a systematic withdrawal procedure. The decision to start withdrawing ASMs was dependent on the participants' characteristics and preferences, which could lead to increased data variability. This approach reflects a real-life clinical setting and makes the models applicable to various realistic withdrawal protocols. The models should only be applied to those who are already considered potential candidates for ASM withdrawal by their treating physicians.

There were baseline differences between the included cohorts, but this reflects real-life scenarios and supports the model's generalizability to a wide range of cohorts and settings. Data on missed medications was unavailable in some cohorts, which could account for provoked seizure relapse. Lastly, due to the large variability of treatment regimens, we did not differentiate or adjusted for specific ASMs or percentage and rate of dose reduction. Future controlled studies are needed to identify the impact of different dose reduction protocols with recurrence risks.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

In summary, we developed and validated simple algorithms that can help assert decisions on postsurgical ASM withdrawal. They might support individuals and attending physicians by providing quantitative risk estimates of seizure relapse that are dependent on the timing of starting ASM withdrawal and are a step towards more personalized epilepsy care.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Acknowledgements

CFA and MG had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. This work was carried out at University College London Hospitals Comprehensive Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's National Institute for Health Research centres funding scheme. AS is supported by the NIHR Oxford Biomedical Research Centre. The RACP Foundation Margorie Hooper Scholarship supports AK. JWS receives support from the Dr Marvin Weil Epilepsy Research Fund, UK Epilepsy Society, Christelijke Vereniging voor de Verplegingvan Lijders aan Epilepsie (Netherlands). Special thanks to Harry Marr BSc (Director of Software Engineering at GitHub) for his technical assistance in creating the website. No compensation was provided, and permission granted to include his name.

Funding

No funding was received towards this work.

Competing interests

MG reports fees and travel support from Bial pharmaceutical and Nestlé Health Science outside the submitted work. PP has received speaker honoraria or consultancy fees to his institution from Chiesi, Eisai, LivaNova, Novartis, Sun Pharma, Supernus, and UCB Pharma, outside the submitted work. He is an Associate Editor for Epilepsia Open. JSD is on the Editorial Board of Annals of Neurology. JWS has received speaker honoraria or consultancy fees from Eisai, UCB Pharma, Arvelle and Zogenix Pharma; grants from Eisai, UCB Pharma

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

outside the submitted work and is on the Editorial Board of the Lancet Neurology, ST is supported by the Susan S Spencer Clinical Research Training Scholarship and the Michigan Institute for Clinical and Health Research J Award UL1TR002240.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

References

1. de Tisi J, Bell GS, McEvoy FRCS AW, et al. *The Long-Term Outcome of Adult Epilepsy Surgery, Patterns of Seizure Remission, and Relapse: A Cohort Study*. Vol 378.; 2011. doi:10.1016/S0140-6736(11)60890-8

2. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *The Lancet Neurology*. 2012;11(9):792-802. doi:10.1016/S1474-4422(12)70153-9

3. Kerling F, Pauli E, Lorber B, et al. Drug withdrawal after successful epilepsy surgery: how safe is it? *Epilepsy Behav*. 2009;15(4):476-480. doi:10.1016/j.yebeh.2009.05.016

4. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomized trials. *The Lancet Neurology*. 2011;10(11):961-968. doi:10.1016/S1474-4422(11)70193-4

5. Lamberink HJ, Otte WM, Geleijns K, Braun KPJ. Antiepileptic drug withdrawal in medically and surgically treated patients: A meta-analysis of seizure recurrence and systematic review of its predictors. *Epileptic Disorders*. 2015;17(3):211-228. doi:10.1684/epd.2015.0764

6. Tellez-Zenteno JF, Hernandez-Ronquillo L, Moien-Afshari F. Discontinuation of antiepileptic drugs after successful surgery: who and when? *Epileptic Disord*. 2012;14(4):363-370. doi:10.1684/epd.2012.0538

7. Rathore C, Jeyaraj MK, Dash GK, et al. Outcome after seizure recurrence on antiepileptic drug withdrawal following temporal lobectomy. *Neurology*. 2018;91(3):e208-e216. doi:10.1212/WNL.0000000000005820

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

8. Menon R, Rathore C, Sarma SP, Radhakrishnan K. Feasibility of antiepileptic drug withdrawal following extratemporal resective epilepsy surgery. *Neurology*. 2012;79(8):770-776. doi:10.1212/WNL.0b013e3182644f7d

9. Ziemba KS, Wellik KE, Hoffman-Snyder C, Noe KH, Demaerschalk BM, Wingerchuk DM. Timing of antiepileptic drug withdrawal in adult epilepsy patients after neocortical surgical resection: a critically appraised topic. *Neurologist*. 2011;17(3):176-178. doi:10.1097/NRL.0b013e318217368e

10. Maehara T, Ohno K. Preoperative factors associated with antiepileptic drug withdrawal following surgery for intractable temporal lobe epilepsy. *Neurol Med Chir (Tokyo)*. 2011;51(5):344-348. doi:10.2176/nmc.51.344

11. Lamberink HJ, Boshuisen K, Otte WM, Geleijns K, Braun KPJ. Individualized prediction of seizure relapse and outcomes following antiepileptic drug withdrawal after pediatric epilepsy surgery. *Epilepsia*. 2018;59(3):e28-e33. doi:10.1111/epi.14020

12. Yardi R, Irwin A, Kayyali H, et al. Reducing versus stopping antiepileptic medications after temporal lobe surgery. *Ann Clin Transl Neurol*. 2014;1(2):115-123. doi:10.1002/acn3.35

13. Lamberink HJ, Otte WM, Geerts AT, et al. Individualized prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *The Lancet Neurology*. 2017;16(7):523-531. doi:10.1016/S1474-4422(17)30114-X

14. Gloss D, Pargeon K, Pack A, et al. Antiseizure Medication Withdrawal in Seizure-Free Patients: Practice Advisory Update Summary. *Neurology*. 2021;97(23):1072-1081. doi:10.1212/WNL.0000000000012944

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

15. Beghi E, Giussani G, Grosso S, et al. Withdrawal of antiepileptic drugs: Guidelines of the Italian League Against Epilepsy. *Epilepsia*. 2013;54:2-12. doi:10.1111/epi.12305

16. Strozzi I SJ. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database of Systematic Reviews*. 2015;(2).

17. Wieser HG, Blume WT, Fish D, et al. *ILAE Commission Report Proposal for a New Classification of Outcome with Respect to Epileptic Seizures Following Epilepsy Surgery Commission on Neurosurgery of the International League Against Epilepsy (ILAE) 1997-2001*. Vol 42.; 2000:282-286.

18. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol*. 2016;69:245. doi:10.1016/J.JCLINEPI.2015.04.005

19. Tigaran S, Cascino GD, McClelland RL, So EL, Richard Marsh W. Acute Postoperative Seizures after Frontal Lobe Cortical Resection for Intractable Partial Epilepsy. *Epilepsia*. 2003;44(6):831-835. doi:10.1046/j.1528-1157.2003.56402.x

20. Bower CM, Hays RD, Devinsky O, et al. Expectations prior to epilepsy surgery: an exploratory comparison of men and women. *Seizure*. 2009;18(3):228-231. doi:https://dx.doi.org/10.1016/j.seizure.2008.09.001

21. Berg AT, Vickrey BG, Langfitt JT, et al. The multicenter study of epilepsy surgery: recruitment and selection for surgery. *Epilepsia*. 2003;44(11):1425-1433.

22. Schmidt D, Baumgartner C, Löscher W, Loscher W, Wolfgang L. Seizure recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: a

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

review of current clinical experience. *Epilepsia*. 2004;45(2):179-186. doi:10.1111/j.0013-9580.2004.37803.x

23. Vickrey BG, Hays RD, Engel J, et al. Outcome assessment for epilepsy surgery: the impact of measuring health-related quality of life. *Ann Neurol*. 1995;37(2):158-166. doi:10.1002/ANA.410370205

24. Hodges S, Goldenholz DM, Sato S, Theodore WH, Inati S. Postoperative EEG association with seizure recurrence: Analysis of the NIH epilepsy surgery database. *Epilepsia Open*. 2018;3(1):109-112. doi:10.1002/epi4.12097

25. Galovic M, van Dooren VQH, Postma TS, et al. Progressive Cortical Thinning in Patients with Focal Epilepsy. *JAMA Neurology*. 2019;76(10):1230-1239. doi:10.1001/jamaneurol.2019.1708

26. Cavanaugh JE, Neath AA. The Akaike information criterion: Background, derivation, properties, application, interpretation, and refinements. *Wiley Interdisciplinary Reviews: Computational Statistics*. 2019;11(3):e1460. doi:10.1002/wics.1460

27. van Smeden M, Reitsma JB, Riley RD, Collins GS, Moons KG. Clinical prediction models: diagnosis versus prognosis. *Journal of Clinical Epidemiology*. 2021;132:142-145. doi:10.1016/J.JCLINEPI.2021.01.009

28. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine*. 1996;15(4):361-387. doi:10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

29. van Smeden M, de Groot JA, Nikolakopoulos S, Bertens LC, Moons KG, Reitsma JB. A generic nomogram for multinomial prediction models: theory and guidance for construction. *Diagnostic and Prognostic Research*. 2017;1(1):8. doi:10.1186/s41512-017-0010-5

30. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med*. 2015;162(1):55-63. doi:10.7326/M14-0697

31. Tellez-Zenteno JF, Ronquillo LHHH, Jette N, et al. Discontinuation of antiepileptic drugs after successful epilepsy surgery. a Canadian survey. *Epilepsy Res*. 2012;102(1-2):23-33. doi:10.1016/j.eplepsyres.2012.04.018

32. He RQ, Zeng QY, Zhu P, Bao YX, Zheng RY, Xu HQ. Risk of seizure relapse after antiepileptic drug withdrawal in adult patients with focal epilepsy. *Epilepsy Behav*. 2016;64(Pt A):233-238. doi:10.1016/j.yebeh.2016.08.006

33. Gasparini S, Ferlazzo E, Giussani G, et al. Rapid versus slow withdrawal of antiepileptic monotherapy in 2-year seizure-free adult patients with epilepsy (RASLOW) study: a pragmatic multicentre, prospective, randomized, controlled study. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2016;37(4):579-583. doi:10.1007/s10072-016-2483-3

34. Park KI, Lee SKSY, Chu K, et al. Withdrawal of antiepileptic drugs after neocortical epilepsy surgery. *Ann Neurol*. 2010;67(2):230-238. doi:10.1002/ana.21884

35. Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

observational study. *Lancet Neurol*. 2012;11(9):784-791. doi:10.1016/S1474-4422(12)70165-5

36. Zhang L, Jiang XY, Zhou D, Zhang H, Bao SM, Li JM. Postoperative seizure outcome and timing interval to start antiepileptic drug withdrawal: A retrospective observational study of non-neoplastic drug resistant epilepsy. *Sci Rep*. 2018;8(1):13782. doi:10.1038/s41598-018-31092-3

37. Fairclough S, O'Keeffe AG, De Tisi J, Duncan JS. Focal-aware seizures and the risk of seizures with impaired consciousness following epilepsy surgery: Implications for driving. *Journal of Neurology, Neurosurgery and Psychiatry*. 2018;89(6):599-602. doi:10.1136/jnnp-2017-316578

38. Lopes MA, Richardson MP, Abela E, et al. An optimal strategy for epilepsy surgery: Disruption of the rich-club?. Daunizeau J, ed. *PLoS Comput Biol*. 2017;13(8):e1005637. doi:https://dx.doi.org/10.1371/journal.pcbi.1005637

39. Lamberink HJ, Otte WM, Blümcke I, et al. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. *The Lancet Neurology*. 2020;19(9):748-757. doi:10.1016/S1474-4422(20)30220-9

40. Tonini C, Beghi E, Berg ATT, et al. Predictors of epilepsy surgery outcome: a meta-analysis. *Epilepsy Res*. 2004;62(1):75-87. doi:10.1016/j.eplepsyres.2004.08.006

41. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: A cohort study. *The Lancet*. 2011;378(9800):1388-1395. doi:10.1016/S0140-6736(11)60890-8

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

42. Bjellvi J, Olsson I, Malmgren K, Wilbe Ramsay K. Epilepsy duration and seizure outcome in epilepsy surgery: A systematic review and meta-Analysis. *Neurology*. 2019;93(2):E159-E166. doi:10.1212/WNL.0000000000007753

43. van Calster B, McLernon DJ, van Smeden M, et al. Calibration: The Achilles heel of predictive analytics. *BMC Medicine*. 2019;17(1):1-7. doi:10.1186/S12916-019-1466-7/TABLES/1

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Table 1. Multivariable Cox regression analysis of time to non-aura recurrence reccurence after beginning of ASM withdrawal following epilepsy surgery.

Predictors	**aHR (95% CI)**	**p-value**	**Δ AIC***
Auras after surgery before beginning ASM withdrawal	5.53 (2.74-11.15)	<0.0001	-14.1
Time to beginning of ASM withdrawal *(per year from surgery)*	0.90 (0.82-0.98)	0.02	-4.8
Focal to bilateral tonic- clonic seizures before surgery	1.60 (0.91-2.82)	0.09	-1.0
Number of ASMs at time of surgery	1.24 (0.95-1.60)	0.10	-0.5
Normal presurgical MRI	eliminated step 5	0.45	1.5
Age at surgery	eliminated step 4	0.59	1.7
Presurgical seizure frequency *(as an ordinal scale)*	eliminated step 3	0.60	1.7
Hippocampal sclerosis on neuropathology	eliminated step 2	0.67	1.8
Duration of epilepsy at time of surgery	eliminated step 1	0.74	1.9

N=231. aHR, adjusted hazard ratio; MRI, magnetic resonance imaging; ΔAIC=change in Akaike information criterion after elimination of a variable at each step; * A negative value implies that the variable improves the model and should be kept in the model.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

Figure legends

Figure 1. Impact of predictors on Kaplan-Meier estimates (time to non-aura seizure recurrence after starting ASM withdrawal)

Panel **A** represents the Kaplan-Meier estimates of time to non-aura seizure recurrence in the overall cohort (n=850). Panels **B-E** show the impact of predictors included in the final model on the time to non-aura seizure recurrence . Time at baseline was beginning of ASM withdrawal. Shaded band represents 95% confidence interval.

Figure 2. Impact of predictors on Kaplan-Meier estimates (time to any seizure recurrence after starting ASM withdrawal)

Panel A represents the Kaplan-Meier estimates of time to any seizure recurrence in the completely seizure-free cohort (n=639). Panels **B-F** show the impact of predictors included in the final model on the time to any seizure recurrence. Time at baseline was beginning of ASM withdrawal. Shaded band represents 95% confidence interval.

Figure 3. Nomograms for predicting 2- and 4-year seizure outcome after starting ASM withdrawal following epilepsy surgery

Freedom from non-aura seizures (**A**) and from any seizures including focal non-motor aware seizures (**B**) after starting ASM withdrawal after epilepsy surgery. Instructions: Determine the individual risk in three steps: 1) For every variable on the left, count the points given at

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

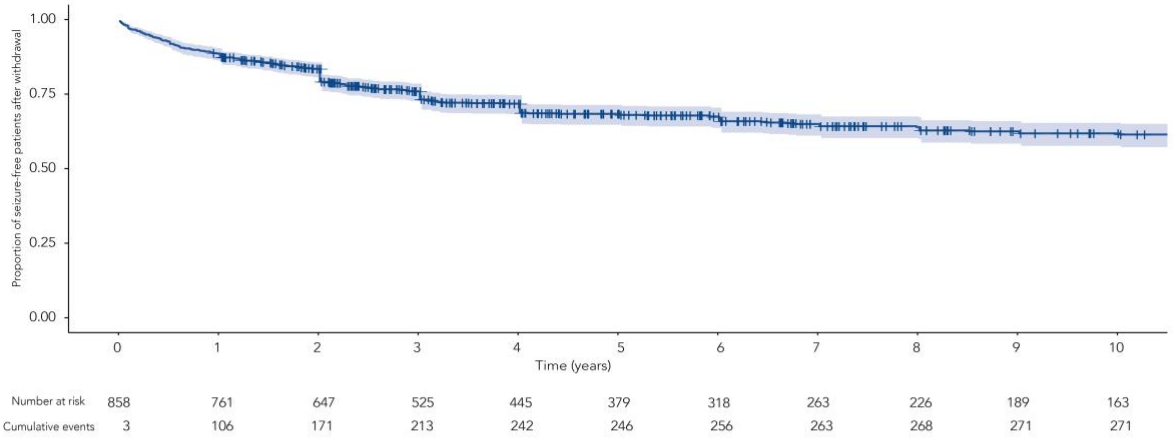
the top, 2) Add up the points to a total, 3) Determine the associated recurrence risk at 2 and 4 years according to the calculated point total.

Figure 4. Fictional case simulations

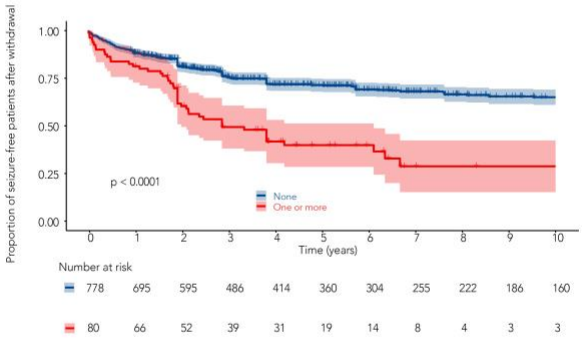
Examples on how to use the nomogram (**A1, B1**) and online tool (**A2, B2**) based on two fictional cases reflecting real life scenarios. Case A (panels **A1-2**) is a 35-year-old individual with a 20-year history of epilepsy with 1-2 preoperative FBTCS per year, no febrile seizures, taking two ASMs at time of surgery, and focal non-motor aware seizures after surgery, who is considering withdrawal of ASMs two years after epilepsy surgery. The models show a low chance of remaining free from non-aura seizures four years after starting withdrawal (35%, 95% CI 20-62). Case B (panels B1-2) is an individual with similar characteristics but no history of FBTCS and complete postoperative seizure-freedom (i.e. no focal non-motor aware seizures after surgery). The models predict a higher chance of remaining seizure-free (freedom from non-aura seizures after four years 86%, 95% CI 80-92; complete seizure freedom after four years 83%, 95% CI 77-88).

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

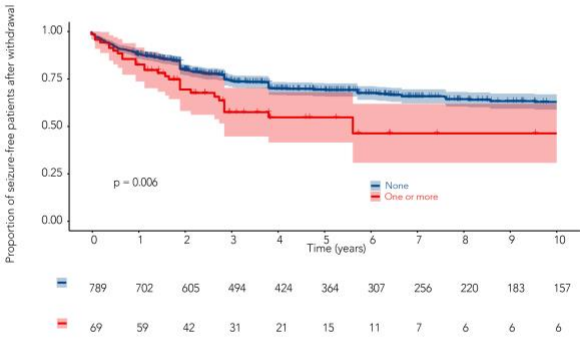
A. Time to seizure relapse after starting ASM withdrawal, overall cohort



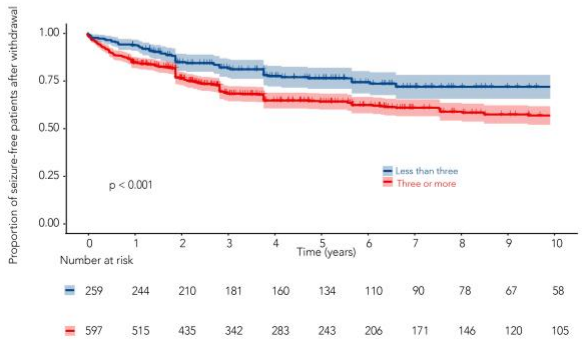
B. Auras after surgery and before ASM withdrawal



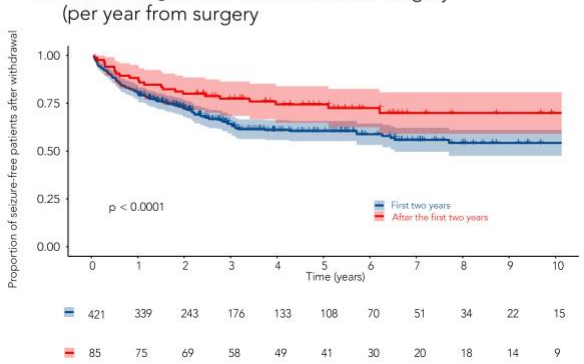
C. Focal to bilateral tonic clonic seizures before surgery



D. Number of ASMs at time of surgery

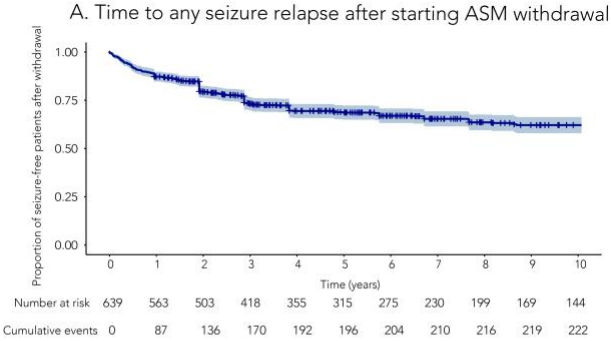


E. Time to begin ASM withdrawal after surgery (per year from surgery

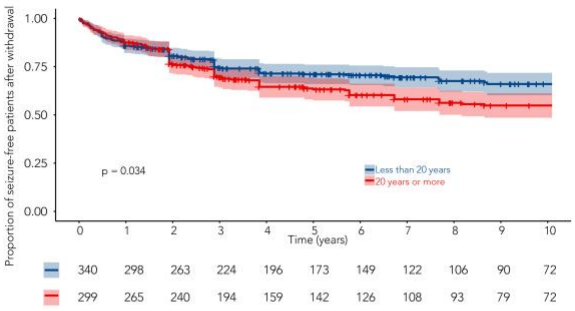


medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. All rights reserved. No reuse allowed without permission.

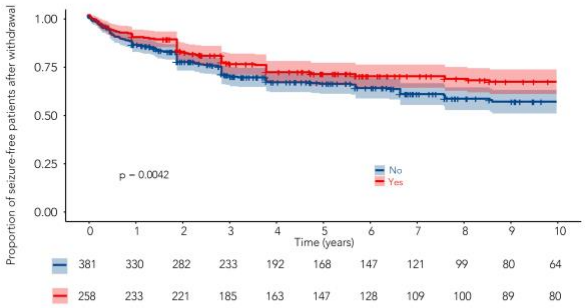
A. Time to any seizure relapse after starting ASM withdrawal



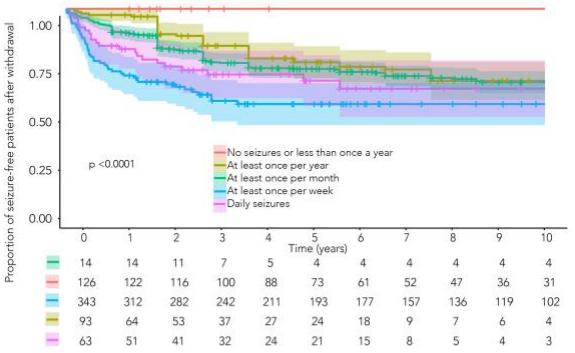
B. Duration of epilepsy at time of surgery (per 10 years)



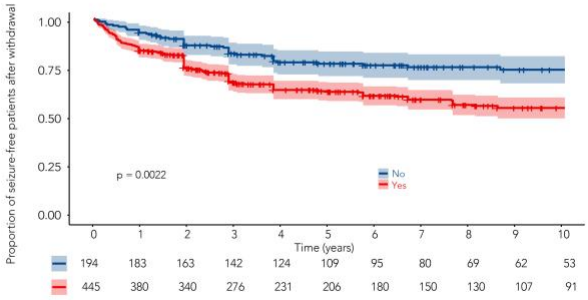
C. History of febrile seizures



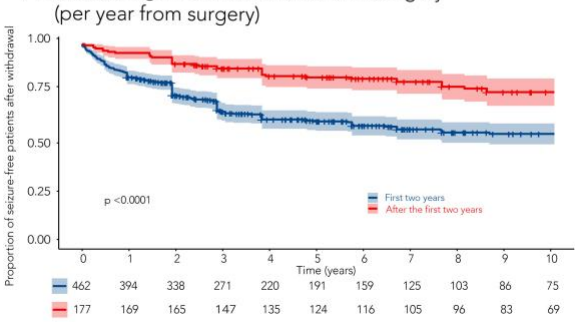
D. Presurgical seizure frequency (as an ordinal scale)



E. Focal to bilateral tonic clonic seizures before surgery

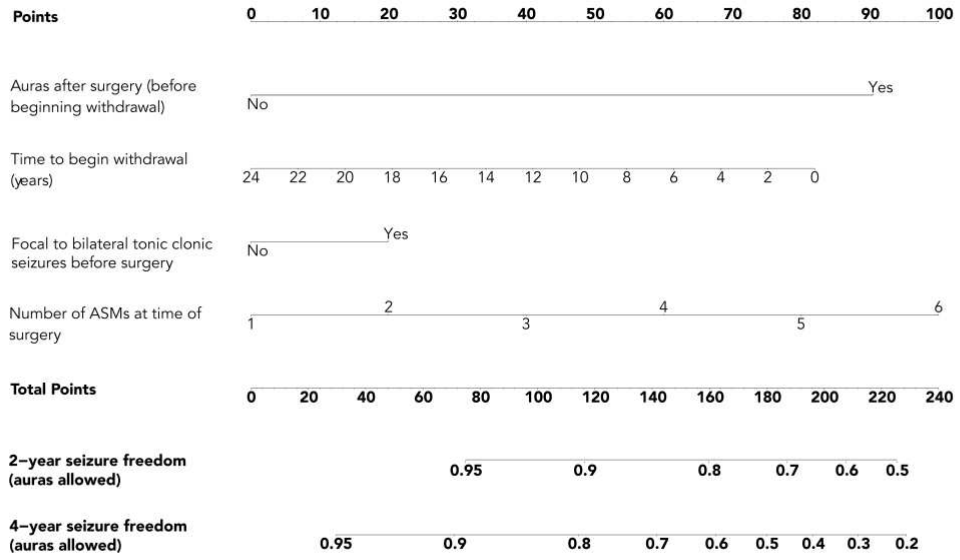


F. Time to begin ASM withdrawal after surgery (per year from surgery)

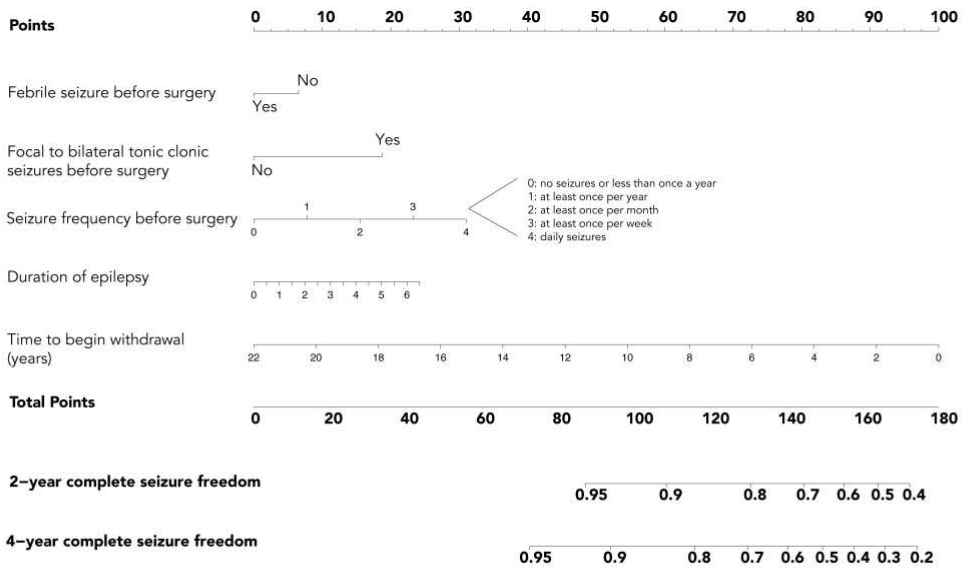


medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

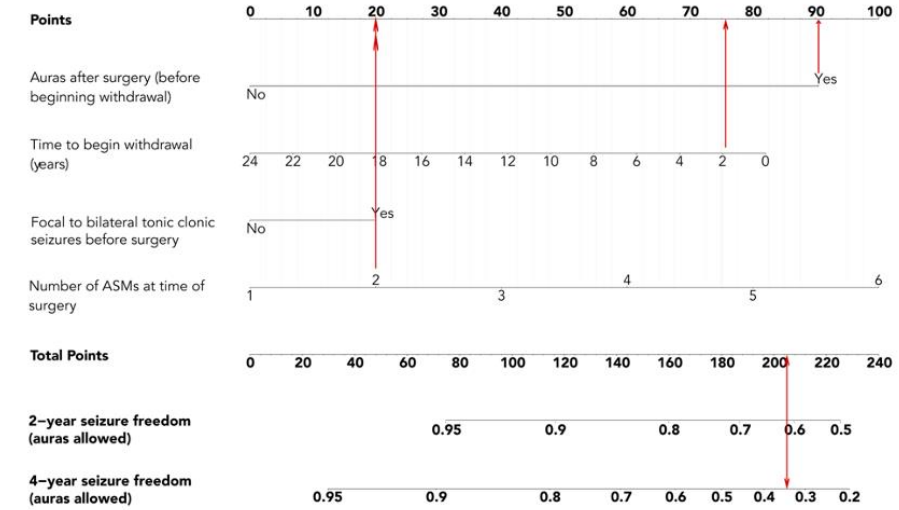
A.



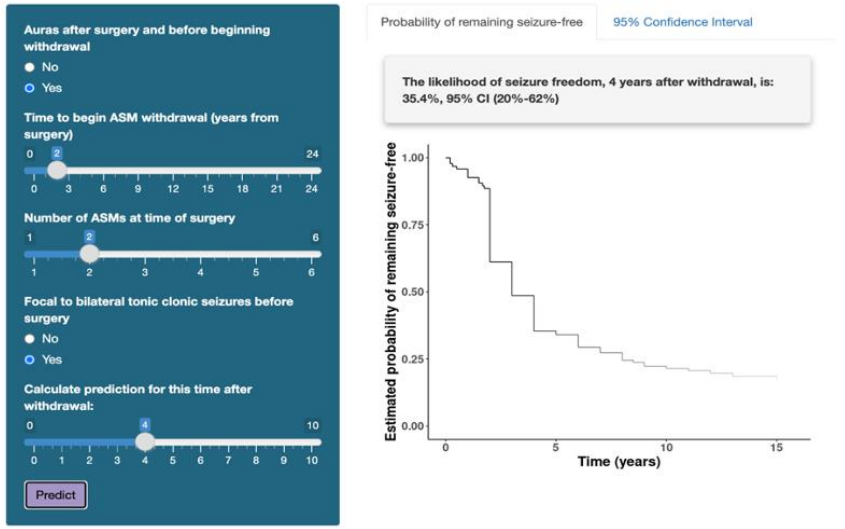
B.



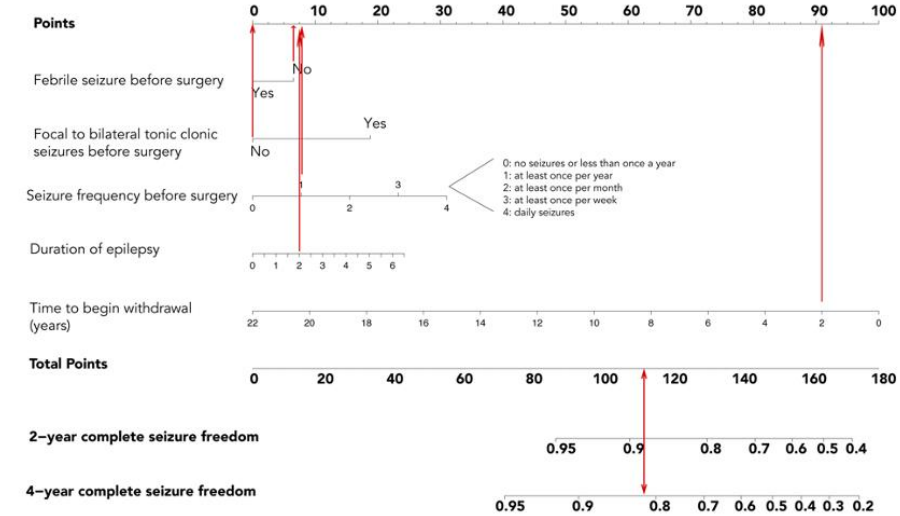
A1.



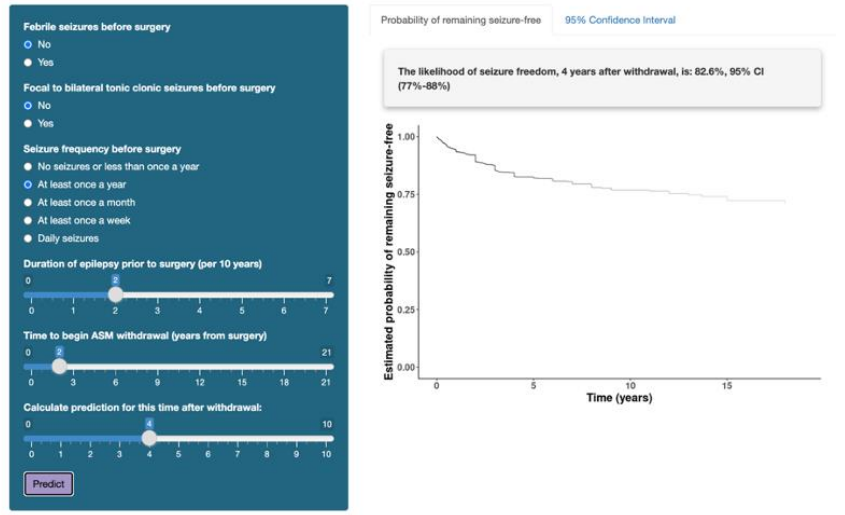
A2.



B1.



B2.



medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.

medRxiv preprint doi: https://doi.org/10.1101/2022.07.22.22277802; this version posted July 26, 2022. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
All rights reserved. No reuse allowed without permission.