Development and validation of a predictive model for seizure recurrence following discontinuation of antiseizure medication in children with epilepsy: a systematic review and meta-analysis, and prospective cohort study

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Summary

Background Seizure relapse in pediatric patients with epilepsy after antiseizure medication (ASM) withdrawal is a critical concern, yet the risk factors are not fully understood. Identifying these factors is essential for personalized treatment planning.

Methods In this systematic review and meta-analysis, and prospective cohort study, we conducted a meta-analysis of cohort studies to derive a predictive model for seizure recurrence post-ASM discontinuation, then validated it in a prospective cohort study. The derivation cohort was derived from a systematic, search of PubMed, Web of Science, Embase, and Cochrane Library (from inception to May 1,2024) for English-language cohort studies on risk factors for seizure recurrence after ASM withdrawal in pediatric epilepsy, focusing on children initiating ASM tapering with documented relapse, while excluding case reports, and non-pharmacological interventions. Risk factors were selected and weighted according to the statistical significance of pooled relative risks (RRs), with β coefficients derived from log-transformed RRs to establish weighted scores in the predictive model. The validation cohort included children with epilepsy enrolled between February 16, 2015 and November 15, 2024, from two Chinese hospitals. Inclusion criteria comprised first-time ASM withdrawal candidates aged <18 years with ≥24-month follow-up, while exclusion criteria focused on incomplete data, protocol deviations, and non-pharmacological interventions. This study is registered at https://www.medicalresearch.org.cn/ (MR-50-24-042059).

Findings A total of 26 cohort studies were identified from the systematic review and included in the meta-analysis. The derivation cohort included 4080 children with epilepsy, of whom 959 (23.50%) experienced seizure recurrence. The predictive model identified nine significant risk factors: intellectual disability, abnormal neurological examination or motor deficit, history of febrile seizures, only focal onset seizures, overall number of ASM used, duration of epilepsy ≥3 years, abnormal electroencephalogram (EEG) at the start of ASM tapering, abnormal EEG after ASM tapering, and age at first seizure ≥10 years. β coefficients were derived from the logarithm of pooled relative risks for each factor and converted into weighted scores, yielding a maximum total risk score of 17. The validation cohort comprised 341 patients with a median follow-up duration of 2.84 (0.27–9.75) years, and 122 (35.8%) out of them had seizure relapses. The model demonstrated robust performance in the validation cohort, with an AUC of 0.85 (95% CI: 0.81–0.91), sensitivity of 0.74 (95% CI: 0.68–0.80), and specificity of 0.82 (95% CI: 0.75–0.89).

Interpretation Our evidence-based predictive model offers a robust tool for estimating the risk of seizure recurrence in pediatric patients with epilepsy after ASM withdrawal, aiding clinicians in personalized treatment decisions. While

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Translation For the Chinese translation of the abstract see Supplementary Materials section.

this tool enhances personalized treatment decisions in epilepsy management, its predictive thresholds require external validation across diverse clinical settings and populations to ensure broad clinical applicability.

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Keywords: Children with epilepsy; Medication withdrawal; Seizure recurrence; Predictive model; Antiseizure medication

Research in context

Evidence before this study

We searched four databases—PubMed, Web of Science, Embase, and the Cochrane Library—for articles published from the inception of each database to April 2024, using the search terms "child" AND "epilepsy" AND "withdrawal" AND "recurrence" AND "seizure free" AND "cohort study". Compared to adults, the clinical complexity of pediatric epilepsy is significantly greater, characterised by a broader spectrum of seizure types, epilepsy syndromes, and etiologies. Currently, the evidence involving the risk factors predicting seizure recurrence in real-world pediatric cohorts remains fragmented, with heterogeneous and often contradictory findings.

Added value of this study

The predictive model identified nine significant risk factors: intellectual disability, abnormal neurological examination or motor deficit, history of febrile seizures, only focal onset seizures, overall number of antiseizure medication (ASM) used, duration of epilepsy ≥3 years, abnormal electroencephalogram (EEG) at the start of ASM tapering, abnormal EEG after ASM tapering, and age at first seizure ≥10 years. Each factor was assigned a weighted score, with a maximum total score of 17. Elevated risk scores are significantly associated with an increased likelihood of seizure recurrence. The model demonstrated robust performance with an AUC of 0.85, sensitivity of 0.74, and specificity of 0.82 in an external validation cohort.

Implications of all the available evidence

This predictive model offers a valuable tool to optimize individualised ASM withdrawal decisions for children by quantifying seizure recurrence risks. While enhancing personalised epilepsy care, its thresholds require external validation in diverse populations and settings to ensure clinical generalisability.

Introduction

Epilepsy is a chronic neurological disorder affecting over 50 million individuals globally, irrespective of age and sex.[1–3] The incidence of epilepsy is particularly high among children compared to other age groups.[4] Aaberg et al. reported a cumulative incidence of epilepsy of 0.66% by 10 years of age, with the highest incidence occurring during infancy.[5] This condition poses a substantial disease and societal burden on children and adolescents worldwide.

Antiseizure medications (ASMs) are the cornerstone of epilepsy management, effectively suppressing seizures in 65%–85% of affected individuals,[6] with approximately 63.7% of patients on ASMs achieving at least one year of seizure freedom.[7] However, up to 88% of patients experience a wide range of adverse effects,[8,9] with the gradual reduction and eventual discontinuation of ASMs often necessary when prolonged seizure freedom is attained. Despite this necessity, there is no definite consensus on the optimal timing or method for safely discontinuing medication, particularly in children, where the risks of seizure relapse and sudden unexpected death in epilepsy (SUDEP) remain significant concerns.[10]

Lamberink et al. have developed nomograms for predicting seizure recurrence after withdrawal ASMs, that presented robust performance when applied to children and adults.[11] Compared to adults, the clinical complexity of pediatric epilepsy is significantly greater, characterised by a broader spectrum of seizure types, epilepsy syndromes, and etiologies.[12] Consequently, the factors influencing seizure outcomes following ASM discontinuation in children are expected to differ significantly. Currently, the evidence involving the risk factors predicting seizure recurrence in real-world pediatric cohorts remains fragmented, with heterogeneous and often contradictory findings.[13–15]

This study aimed to address these gaps by developing a predictive model for seizure recurrence following ASM discontinuation in children with epilepsy. The model was derived from a meta-analysis of published cohort studies and subsequently validated using data from two tertiary pediatric medical centres. The objective was to create an evidence-based tool to predict seizure outcomes, enabling clinicians and families to make informed decisions regarding ASM withdrawal while minimizing the risks of adverse outcomes associated with seizure recurrence.

Methods

Study populations

Derivation cohort

The derivation cohort was established using patient data sourced through systematic reviews and meta-analyses. A comprehensive literature search was conducted across four databases—PubMed, Web of Science, Embase, and the Cochrane Library—to identify relevant English-language studies addressing risk factors for seizure relapse following ASM discontinuation in pediatric epilepsy. The search, covering all records from the inception of each database to April 2024, employed a combination of text keywords and MeSH headings, including "child", "epilepsy", "withdrawal", "recurrence", "seizure free", and "cohort study". Detailed search queries are provided in the Supplementary Methods.

To ensure relevance and rigor, the inclusion criteria required studies to: (1) focus exclusively on pediatric epilepsy cohorts, (2) report seizure recurrence outcomes following ASM withdrawal, and (3) provide risk ratios (RRs) with corresponding 95% confidence intervals (CIs) for identified risk factors, either directly or derived through data transformation. Studies involving surgical interventions or non-ASM treatments, such as vagus nerve stimulation, prior to withdrawal were excluded to maintain consistency in the dataset. K. Dai and D. Tang independently conducted the literature search and data extraction. Any discrepancies were resolved through discussion with the senior author, T. Li, to ensure consensus. The methodological quality of each study was evaluated using the Newcastle–Ottawa Scale, a validated tool for assessing nonrandomized studies. This ensured the inclusion of high-quality data, reducing potential biases.[16]

Validation cohort

The validation cohort comprised pediatric patients recruited from the Children's Hospital of Chongqing Medical University (CHCMU) and Kunming Children's Hospital (KMCH). These children were diagnosed with epilepsy and initiated ASM tapering between 16 February 2015 and 15 November 2024. The study focused on first-time ASM discontinuation, with specific inclusion and exclusion criteria designed to ensure the robustness and reliability of the dataset. Eligible patients met the following inclusion criteria: (1) age under 18 years at the time of ASM tapering; (2) seizure recurrence documented during the follow-up period or a minimum follow-up duration of 24 months regardless of relapse; and (3) no prior history of ASM withdrawal. Exclusion criteria included: (1) incomplete demographic and clinical data; (2) lost to follow-up before seizure recurrence; (3) patients unable to complete the planned tapering process with resumption of prior anti-seizure medications; (4) cases receiving epilepsy surgery or other non-ASM treatments. (5) failure to comply with sequential ASM discontinuation protocol (3–6 months per ASM) in children on multiple ASMs.

Participants were prospectively monitored at regular intervals of 3–6 months through outpatient visits or WeChat interviews. Clinical data were systematically recorded, including date of ASM withdrawal initiation, timing of any recurrent seizures, and electroencephalogram (EEG) recordings following ASM weaning. The seizure semiology was assessed by epilepsy diary and/or videos by cellphone from the patients and caregivers carefully.

Outcome

The primary outcome of this study was the recurrence of epileptic seizures in children following the initiation of ASM withdrawal. We adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis–Artificial Intelligence (TRIPOD-AI) reporting guidelines to ensure the rigorous and comprehensive presentation of our study.

Ethics statement

This study was approved by the Ethics Committees of CHCMU (2022 NO·225) and KMCH (2024-03-206-K01). Informed consent was obtained from the parents or guardians of all study participants, and assent was obtained from the participants themselves where applicable. This study has been registered at https://www.medicalresearch.org.cn/ (MR-50-24-042059).

Meta-analysis and model development

The risk factors were screened and identified by the meta-analyses and related statistical evaluations using Stata v18.0 and R software. Briefly, statistical analysis was conducted on all risk factors identified in the cohorts that met the inclusion criteria. Considering the clinical relevance and research attention, the 10 most frequently reported risk factors, based on the number of studies addressing each factor, were selected for further evaluation. For the selected risk factors, RRs and their corresponding 95% CIs were extracted from the included cohorts. The choice between a random-effects model or a fixed-effects model was determined by the level of heterogeneity, assessed using the Cochrane Q test and quantified through the I^2 statistic. An I^2 value exceeding 50% or a *P*-value below 0.10 in the Cochrane Q test indicated significant heterogeneity, prompting the use of a random-effects model. In instances where such heterogeneity is detected, a random-effects model is employed. In the absence of such heterogeneity, a fixed-effects model was utilized. Subgroup analyses were performed to account for different approaches to treating continuous variables and sensitivity analyses were conducted to assess the robustness of the pooled results by modifying the model selection criteria between random-effects and fixed-effects approaches.

Publication bias was evaluated for risk factors reported in more than 10 articles using Egger's linear

regression test and Begg's test, with the significance threshold set to $P < 0.10$. All statistical tests were conducted as two-tailed, with a conventional significance level of $P < 0.05$, except for heterogeneity and publication bias assessments, which were deemed statistically significant at $P < 0.10$.

A classification point system was established using methodologies outlined in previous research and Framingham Study risk score functions.[17,18] Each risk factor included in the model was selected from the statistically significant outcomes of the meta-analysis. Subsequently, pooled RRs for the cited risk factors with statistical significance were extracted according to sensitivity analyses to enhance predictive model functionality. For each risk factor, β-coefficients were calculated using the RRs and their corresponding 95% CIs. The corresponding score for each risk factor was determined by dividing its regression coefficient (β_n) by the smallest absolute value of the coefficients (β_{min}) and rounding to the nearest whole number. This scoring system assigned weighted values to each risk factor, enabling calculation of a total risk score for each patient in the predictive model. Statistical significance was defined as a P-value <0.05.

Model validation

The generalizability and clinical utility of the predictive model were evaluated using external validation data derived from the previously described cohort. To assess the clinical applicability of the model, decision curve analysis (DCA) was performed, providing insight into its clinical utility for guiding clinical decisions.[19] The predictive capability of the model was further evaluated by determining seizure recurrence rates within each risk group and generating Kaplan–Meier (K-M) survival curves for each group to illustrate time-to-recurrence distributions.[20]

All statistical analyses were conducted using IBM SPSS (v27.0, IBM Corp), Stata MP (v18.0, Stata Corp, College Station, TX), and R software (v4.2, R Foundation for Statistical Computing). Graphical outputs, including survival curves and risk stratifications, were generated using R software.

Risk stratification

In order to facilitate the clinical application of the predicted model and tailor the clinical decisions, total risk scores were computed for each patient using baseline variables, with X-tile software (v3.6.1; Yale University, New Haven, USA) applied to ascertain the optimal thresholds for stratifying pediatric patients into low, moderate, and high-risk groups for seizure recurrence following ASM discontinuation.[21]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. K.D., D.T., and T.L. accessed and verified the data. All authors are responsible for the decision to submit the manuscript.

Results

Derivation cohort

Literature search

A total of 778 articles were initially retrieved during the literature search. After excluding duplicates (n = 169) and irrelevant abstracts (n = 532) and full-text articles (n = 48) that did not meet the inclusion criteria, 29 articles were identified that specifically addressed risk factors for seizure relapse. Of these, 26 articles were selected for inclusion in the analysis as they addressed the 10 most frequently cited risk factors, as well as duration of epilepsy (Figure S1). The duration of epilepsy, defined as the interval between the first and last seizure prior to ASM discontinuation regardless of seizure frequency, was included due to its significant-negative correlation with both seizure control[11,22–24] and other relevant negative outcomes.[25,26] The methodology for study selection is depicted in Fig. 1.

Characteristics and quality of included studies

The final analysis included 26 cohort studies,[13–15,27–49] published between 1981 and 2023, encompassing 4080 pediatric patients with epilepsy who discontinued ASMs. Follow-up periods ranged from 0.25 to 17 years. Of the 959 patients (23.50%) who experienced seizure recurrence during the follow-up period, data on the timing of recurrence were available for 526 children.[14,15,30–33,35–39,43–45,47,48] Among these, 83.1% (n = 437) experienced relapse within two years of ASM withdrawal. The studies included cohorts from diverse geographical regions, including Europe (Italy, Netherlands, Greece, United Kingdom, Switzerland, Serbia, Turkey, and Spain), the Americas (United States, Canada, and Brazil), Asia (China and Japan), and Africa (Kenya and Ethiopia). Comprehensive clinical characteristics of the included studies are provided in Table 1, while the examined risk factors are summarized in Table S1. The quality of all 26 studies was assessed using the Newcastle–Ottawa scale, with scores ranging from 7 to 9, indicating high methodological quality. Detailed information on quality assessment indicators is provided in Table S2.

Overall response and sensitivity analysis

The systematic review and meta-analysis synthesized RRs for the 11 established risk factors, with results presented in forest plots (Figures S2–S16). Eight risk factors were consolidated in a forest plot (Fig. 2a), while group analyses were conducted for the remaining three risk factors, stratified according to classifications reported in the included studies (Fig. 2b). To enhance clinical applicability, the most reliable results from

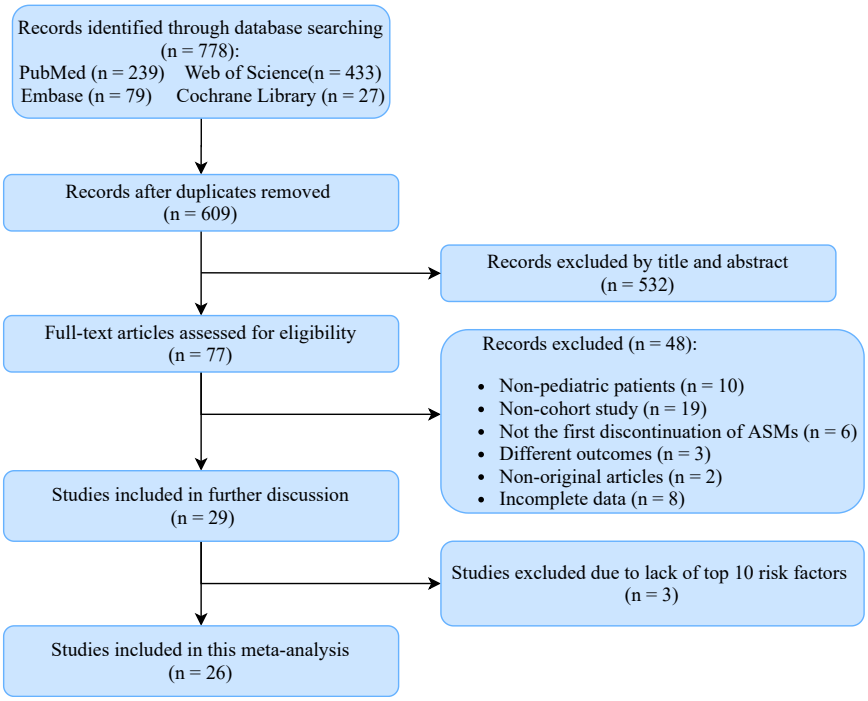

Fig. 1: **Flow diagram of the literature search.**

subgroup and sensitivity analyses were prioritized. Risk factors with a *P*-value ≥0.05, including sex, family history of seizures, and number of epileptic seizures, were excluded from the final model. Ultimately, nine risk factors were statistically significant: intellectual disability (RR 1.771, 95% CI 1.383–2.269; $P < 0.0001$), abnormal neurological examination or motor deficit (RR 1.503, 95% CI 1.122–2.013; $P = 0.0063$), history of febrile seizure (RR 1.535, 95% CI 1.144–2.060; $P = 0.0043$), only focal onset seizures (RR 1.318, 95% CI 1.155–1.504; $P < 0.0001$), overall number of ASMs used (≥2, RR 1.609, 95% CI 1.135–2.28; $P = 0.0075$), duration of epilepsy (≥3 years, RR 1.815, 95% CI 1.231–2.676; $P = 0.0026$), abnormal EEG at the start of ASM tapering (RR 1.649, 95% CI 1.282–2.122; $P = 0.0001$), abnormal EEG after ASM tapering (RR 2.578, 95% CI 1.817–3.657; $P < 0.0001$), and age at first seizure (<10 years, RR 0.526, 95% CI 0.352–0.787; $P = 0.0018$). Detailed definitions of each risk factor are provided in the Supplementary Materials under "notes".

Publication bias

Potential publication bias was assessed for risk factors evaluated in studies with at least 10 included articles. Funnel plots for all analysed risk factors demonstrated satisfactory symmetry (Figures S17–S24), suggesting minimal likelihood of publication bias. To confirm this finding, both Egger's test and Begg's test were performed, neither of which yielded statistically significant results (Table S3), affirming the absence of publication bias.

Model development

The RRs for all 11 selected predictive factors are presented in Fig. 2. Variables including sex, family history, and number of seizures were excluded due to a lack of statistical significance. Ultimately, 8 predictors were retained, with EEG findings further categorized as abnormal EEG at the start of and after ASM tapering. The pooled RRs for the risk factor of "age at onset" was less than 1, resulting in a negative score. To maintain clinical relevance and enhance practical applicability, the scoring criteria for this factor were adjusted to ensure a positive score. Consequently, a straightforward risk predictive model for pediatric epilepsy following the cessation of medication was developed, as illustrated in Table 2. The total score, calculated by summing scores across all domains, reached a maximum of 17, with a higher cumulative score indicating an increased likelihood of seizure relapse. Given the significant regional variations in the incidence and etiology of childhood epilepsy,[50] as well as the inherent limitations in the populations included in the studies, this model is recommended primarily for pediatric populations in Western and Asian countries, ensuring the reliability and relevance of the model within these demographic contexts.

Given the clinical significance of seizure-free duration prior to ASM tapering,[10,11] this variable was intentionally incorporated into the meta-analysis, despite not ranking among the top 10 factors based on report frequency. However, subsequent analysis demonstrated no

First author, year	Country	Prospective/ Retrospective cohort	Follow-up, yrs mean (range)	Research time	Age at ASM withdrawal (yrs) mean (range)	Case/Simple size	Sex (male/total)	NOS score
Emerson, R 1981[27]	USA	Prospective	0.5–6	1973–1979	6–22	18/68	–	8
Bouma, P A 1987[28]	Holland	Prospective	4.3 (0.75–10)	1972–1984	10 (2.42–19.58)	26/116	63/116	9
Matricardi, M 1989[29]	Italy	Prospective	8 (1.6–12)	1975–1987	11 (4–19)	50/425	241/425	9
Ehrhardt, P 1989[30]	United Kingdom	Retrospective	1–14	1970–1984	–	22/187	103/187	8
GHERPELLI, JLD 1992[31]	Brazil	Prospective	1.54 (0.25–3.58)	1982.2–1985.10	9.5 (4.17–15)	20/70	36/70	8
Mastropaolo, C 1992[32]	Italy	Prospective	3.5 (2–15)	1972–1987	10.1 (1.6–22.2)	43/191	109/191	8
Tennison, M 1994[13]	USA	Prospective	3.25 (0.92–8.75)	–	10.0 (0.1–17)	53/133	70/133	8
Shinnar, S 1994[33]	USA	Prospective	4.83	1983.10–1990.10	11.8	95/264	136/264	9
DONATI, F 1995[34]	Switzerland	Prospective	4 (1.3–9)	1985–1994	10.3 (4.2–18)	24/82	44/82	8
Dooley, J 1996[14]	Canada	Prospective	2.7 (1–4.75)	1989.3.1–1993.2.28	7.25	39/97	50/97	9
Marcus, J C 1998[35]	USA	Prospective	≥2	–	–	12/29	–	8
Zafeiriou, D I 1999[36]	Greece	Prospective	9.2 ± 2.4	–	–	18/255	105/178	8
Gebremariam, A 1999[37]	Ethiopia	Prospective	–	1988.4–1992.9	–	26/90	50/90	7
Altunbasak, S 1999[38]	Turkey	Prospective	(2–4)	1990–1995	12.5 (4–20)	20/97	58/97	8
Verrotti, A 2000 (A)[15]	Italy	Prospective	(5.1–6.7)	–	11.2	24/89	40/89	8
Verrotti, A 2000 (B)[39]	Italy	Prospective	5.5 (4–7)	1997.6–1999.12	10.6 ± 3.0	24/84	–	8
Vurucu, S 2010[40]	Turkey	Retrospective	2	–	–	51/266	155/266	8
Ramos-Lizana, J 2010[41]	Spain	Prospective	4.92	1994.6.1–2004.12.31	4.76 (1–13)	56/216	120/216	9
Pavlovic, M 2012[42]	Serbia	Retrospective	(2–13)	2001.1–2009.12	14 (6–20)	19/52	36/52	8
Lee, I C 2017[43]	Taiwan, China	Retrospective	5	–	11.2 (7–20)	43/107	56/107	8
Karalok, Z S 2020[44]	Turkey	Retrospective	8.3 (3–17)	1997.1–2014.1	–	51/284	147/284	8
Komatsubara, T 2022[45]	Japan	Retrospective	–	2001.1–2020.12	16.4 (10–19)	52/77	41/77	8
Yildirim, M 2022[46]	Turkey	Retrospective	3.83 (1.5–10.5)	2010.1–2020.6	–	90/269	157/269	8
Odero, N 2023[47]	Kenya	Retrospective	≥2	2011.1–2019.12	5.8	13/49	35/49	8
Zhao, Y H 2023[48]	China	Retrospective	≥2	2009.1–2019.12	(2–14)	19/80	45/80	8
Kanmaz, S 2023[49]	Turkey	Retrospective	3.12 ± 2.53 (1–12)	2005–2018	10.4 (3–18)	51/403	222/403	8

Table 1: **Baseline characteristics of the 26 studies.**

statistically significant association, which ultimately excluded it from the final predictive model (Figure S21).

Validation cohort

Study population

Between February 2015 and November 2024, a total of 653 children from CHCMU and KMCH underwent ASM discontinuation. To ensure the broad applicability of the predictive model, all the cases of ASM discontinuation were included, irrespective of the duration of seizure freedom prior to withdrawal. After a rigorous screening process, the validated cohort comprised 341 pediatric patients, 122 of whom experienced seizure relapses. Of the 312 cases excluded, 238 were excluded due to insufficient follow-up time, 26 were lost to follow-up, 13 ceased ASM tapering and resumed to the original regimen due to concerns about recurrence, 29 were excluded due to insufficient baseline data, and six did not meet the diagnostic criteria for epilepsy (Fig. 3).

Within the validated cohort, the median age at tapering ASM was 7.01 years (range, 0.58–17.99 years), 35.8% of participants (n = 122) experienced seizure recurrence. The median time to relapse was 0.58 months (interquartile range: 0.16, 1.13 months). The cohort utilized nine different ASMs, resulting in 453 instances of ASM use. The most frequently administered ASMs were valproic acid (153 instances, 33.8%), levetiracetam (127 instances, 28.0%), oxcarbazepine (77 instances, 17.0%), and benzodiazepines (32 instances, 7.1%). Among the 215 patients diagnosed with epileptic syndromes, 155 (72.1%) were classified as focal onset epileptic syndromes, including self-limited epilepsy with centrotemporal spikes (SeLECTS), accounting for 95 cases (61.3%), followed by self-limited (familial) infantile epilepsy (SeLIE), accounting for 51 cases (32.9%). Of the 341 pediatric patients, etiology was determined in 208 cases, including 193 attributed to genetic causes such as self-limited focal epilepsy syndromes, genetic generalized epilepsies, and identifiable genetic variants, while 15 were attributed to structural causes.[51] Twelve variables, including intellectual disability, age at first seizure, and EEG findings at the onset of tapering, exhibited significant differences between the relapse and no-relapse groups, aligning with the meta-analysis findings. A detailed summary of the characteristics of the validated cohort is provided in Table 3.

Model validation

Prior to model validation, we evaluated the variance inflation factors (VIFs) for all predictors within the

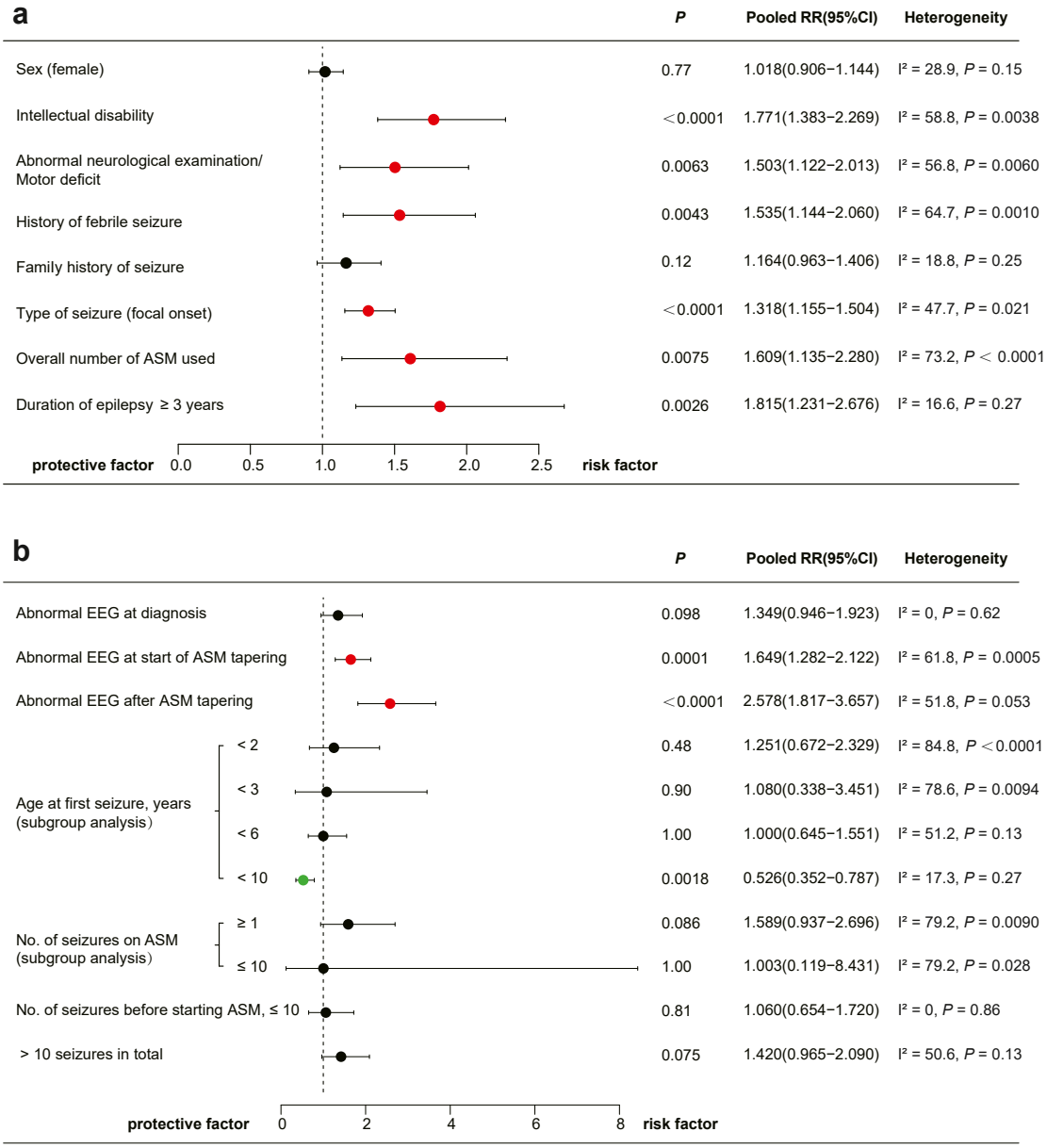

***Fig. 2:* Pooled RRs and corresponding 95% CIs for each risk factor**. a: Pooled RRs and 95% CIs for risk factors, excluding those subjected to subgroup analysis. b: Subgroup or sensitivity analysis of risk factors. Dots represent overall estimates, green indicates protective factors, red indicates risk factors, black indicates statistically insignificant factors. Horizontal bars represent 95% CIs.

validation cohorts. The analysis revealed no significant multicollinearity among the predictors, with all VIF values falling within an acceptable range (<2) (Table S4).

The performance of the relapse predictive model was evaluated using receiver operating characteristic (ROC) curves, as shown in Fig. 4a, with individual ROC curves for each risk factor provided in Figure S25. Analysis revealed that the AUC for the comprehensive model was 0.85 (95% CI: 0.81–0.91), outperforming all individual predictors. The model demonstrated an accuracy of 0.77 (95% CI: 0.72–0.81), a sensitivity of 0.74 (95% CI: 0.68–0.80), a specificity of 0.82 (95% CI: 0.75–0.89), and

Risk factor	Score
Age at first seizure, yrs	
<10	0
≥10	2
Duration of epilepsy, yrs	
<3	0
≥3	2
EEG after ASM tapering	
Normal	0
Abnormal	3
EEG at start of ASM tapering	
Normal	0
Abnormal	2
History of febrile seizure	
No	0
Yes	2
Intellectual disability	
No	0
Yes	2
Abnormal neurological examination or Motor deficit	
No	0
Yes	1
Overall number of ASM used	
1	0
≥2	2
Type of seizure	
Others	0
Only focal onset	1
Total	17

Table 2: **Predictive model for seizure recurrence in pediatric patients.**

a F1 score of 0.804 (95% CI: 0.747–0.860). The calibration curve demonstrated strong concordance between the predictive model and observed outcomes (Fig. 4b). The decision curve (Fig. 4c) demonstrates that using our model to guide clinical decisions provides greater net benefit than 'treat all' or 'treat none' strategies across thresholds of 9–77%. Assuming a clinical intervention threshold of 30%, the model-guided strategy yields a net benefit of 0.22, compared to 0.08 for 'treat all' and 0.00 for 'treat none'. The corresponding risk percentages associated with each sum score is presented in Fig. 4d. The optimal cutoff for the scoring system was determined as 3.5 by maximizing Youden's index, yielding an accuracy of 0.77 (95% CI: 0.72–0.81), sensitivity of 0.74 (0.68–0.80), and specificity of 0.82 (0.75–0.89). For clinical practicality, a score of 4 (representing a recurrence probability of 0.317, 95% CI: 0.257–0.377) was selected as the operational cutoff in the scoring system.

Given the limited availability of EEG recordings, especially in underdeveloped regions, we developed another three prediction models: one excluding EEG findings at the start of ASM tapering, another excluding post-tapering EEG, and a third excluding both. The AUC values were 0.841 (95% CI: 0.802–0.883), 0.749 (95% CI: 0.705–0.793), and 0.694 (95% CI: 0.638–0.755), respectively (see Figure S23). The results suggest that the predictive model maintains clinically meaningful performance even in the absence of EEG data throughout the tapering process, highlighting its potential utility in settings with limited access of EEG. Given that the absence of post-withdrawal EEG data represents the most common scenario, we present a scoring system specifically designed for this context in the Supplementary Materials (Table S5).

To comprehensively evaluate the temporal predictive performance of our model, we conducted a longitudinal analysis comparing key metrics at two critical time points following ASM tapering in the validation cohort. At 2-year and 5-year follow-ups respectively, the model demonstrated similar performance with an AUC of 0.84 (95% CI: 0.79–0.89) versus 0.80 (95% CI: 0.65–0.94), sensitivity of 0.74 (95% CI: 0.68–0.80) versus 0.72 (95% CI: 0.52–0.93), and specificity of 0.82 (95% CI: 0.73–0.91) versus 0.82 (95% CI: 0.59–0.97). All the data between the two time points were comparable, which suggest that the predictive performance of this model is robust during the first 5 years after ASM tapering.

Clinical risk stratification

Utilizing the X-tile program, the 341 patients in the validation cohort were stratified into three distinct risk categories based on their actual total scores: low risk (n = 184, total score ≤3), moderate risk (n = 89, 4 ≤ total score ≤6), and high risk (n = 68, total score ≥7). The K-M curves for the three groups indicated that seizure relapse predominantly occurred within the first two years following ASM discontinuation (Fig. 4e). Compared to the low-risk group, the RR values for relapse were 4.42 (95% CI: 2.85–6.85) for the moderate-risk group and 6.52 (95% CI: 4.32–9.84) for the high-risk group, both statistically significant ($P < 0.0001$). When comparing the high-risk group to the moderate-risk group, the RR value was 1.48 (95% CI: 1.17–1.86), with a *P*-value of 0.0023, also indicating statistical significance. Based on the K-M curves, an increase in the total score corresponds to an increased risk of seizure recurrence. For example, an 8-year-old male with epilepsy presented with focal onset seizures and a one-year interval between the initial and last seizure episodes. There was no history of febrile seizures, and treatment consisted solely of valproic acid, which demonstrated effective seizure control. Neurological and neuropsychological assessments revealed no abnormalities, and motor function was intact. At the start of medication withdrawal, the EEG was unremarkable; however, follow-up EEGs during the tapering period displayed epileptiform activity. The scores assigned to the individual risk factors were 0, 1, 0, 0, 0, 0, 0, 0, and 3, resulting in a total score of 4. This placed the individual in the moderate-risk category, indicating an increased

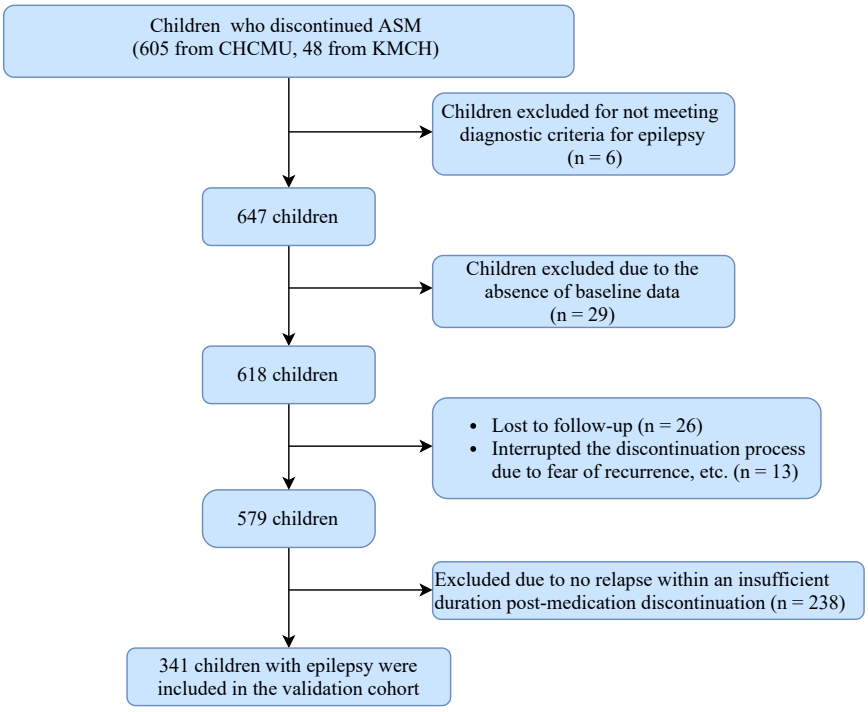

Fig. 3: **Process for patient selection in validation cohort**.

likelihood of seizure recurrence following ASM discontinuation.

Discussion

This study identified nine independent risk factors significantly associated with seizure relapse in children with epilepsy following the discontinuation of ASMs. These findings were derived from a comprehensive meta-analysis of 26 high-quality cohort studies, collectively consisting of 4080 pediatric patients.[13–15,27–49] The proposed predictive model was externally validated using data obtained from two independent hospitals, demonstrating robust clinical applicability in guiding decisions regarding ASM withdrawal in sustained seizure-free children.

Systematic evaluation and meta-analysis,[52] recognized as validated methodologies, were utilized to construct the predictive model in accordance with the guidelines outlined by BMJ,[53] ensuring its reliability and clinical relevance. The validation yielded an AUC of 0.85, with sensitivity and specificity values of 0.81 and 0.89, respectively, indicating strong discriminatory performance. Current evidence demonstrates that the majority of seizure relapses occur within the first 2 years following ASM withdrawal, with a subsequent gradual decline in recurrence rates over time.[54] The validation cohort analysis demonstrated consistent model performance, with comparable AUC values, sensitivity, and specificity between the 2-year and 5-year post-withdrawal periods. These findings indicate that the predictive model maintains robust and stable performance throughout an extended 5-year follow-up period following ASM discontinuation. X-tile was applied to stratify the validation cohort into low-, moderate-, and high-risk groups, with statistically significant differences observed between all risk groups. Overall, this predictive model provides a robust framework for stratifying relapse risk in pediatric patients, enabling clinicians to make informed decisions regarding ASM withdrawal in seizure-free children. Abnormal EEG recordings at the initiation of and during ASM weaning were identified as key factors associated with seizure relapse, emphasizing the critical importance of EEG in assessing recurrence risk. While epileptiform activity on EEG is a well-established predictor of seizure relapse in adults,[11] slow age-inappropriate background activity has also been identified as a significant risk factor in children. Research by Paolo et al. demonstrated that abnormal EEG background activity reflects disease progression in patients with developmental and epileptic encephalopathies (DEE) and is linked to negative clinical outcomes.[55,56] EEG abnormalities following the initiation of ASM tapering, which exhibited the highest AUC (0.79) among risk factors, highlight the necessity for meticulous monitoring of EEG activity during and after weaning. However, as demonstrated in Figure S23-2, risk stratification remains clinically feasible even when

Variable	Total (n = 341)	No-recurrence group (n = 219)	Recurrence group (n = 122)	Statistic	*P*
Sex[a], n (%)				χ^2 = 1.46	0.23
Female	149 (43.70)	101 (46.12)	48 (39.34)		
Male	192 (56.30)	118 (53.88)	74 (60.66)		
Age at first seizure, years, M (Q_1, Q_3)	3.00 (0.90, 7.00)	3.00 (0.82, 6.53)	4.00 (1.10, 7.72)	Z = −2.23	**0.026**
Age at withdrawal of ASMs, years, M (Q_1, Q_3)	7.00 (4.00, 10.49)	6.90 (3.82, 10.29)	7.70 (4.74, 10.86)	Z = −1.18	0.24
Family history of seizure, n (%)				χ^2 = 13.66	**0.0002**
No	313 (91.79)	210 (95.89)	103 (84.43)		
Yes	28 (8.21)	9 (4.11)	19 (15.57)		
History of febrile seizure, n (%)				χ^2 = 8.98	**0.0027**
No	268 (78.59)	183 (83.56)	85 (69.67)		
Yes	73 (21.41)	36 (16.44)	37 (30.33)		
Seizure type, n (%)				χ^2 = 2.89	0.089
Only focal onset	240 (70.38)	161 (73.52)	79 (64.75)		
Others	101 (29.62)	58 (26.48)	43 (35.25)		
Seizure-free duration, months, M (Q_1, Q_3)	28.43 (22.77, 37.27)	30.70 (24.87, 39.60)	23.27 (10.80, 30.29)	Z = −6.83	**<0.0001**
Duration of epilepsy, yrs, M (Q_1, Q_3)	0.29 (0.05, 1.19)	0.25 (0.05, 1.14)	0.43 (0.07, 1.35)	Z = −1.26	0.21
Follow-up time, years, M (range)	2.84 (0.27, 9.75)	2.90 (2.02, 7.67)	2.61 (0.27, 9.75)	–	–
Tapper time, months, M (Q_1, Q_3)	8.32 (5.97, 13.12)	9.12 (6.08, 14.54)	6.73 (5.53, 9.57)	Z = −2.57	**0.010**
Time to recurrence, M (Q_1, Q_3)	–	–	0.58 (0.16, 1.13)	–	–
Overall number of ASM used, n (%)				–	**0.017**
1	253 (74.19)	174 (79.45)	79 (64.75)		
2	70 (20.53)	35 (15.98)	35 (28.69)		
3	13 (3.81)	8 (3.65)	5 (4.10)		
4	4 (1.17)	2 (0.91)	2 (1.64)		
5	1 (0.29)	0 (0.00)	1 (0.82)		
Epilepsy syndrome, n (%)				χ^2 = 11.83	**0.0080**
DEE or PNDs	24 (7.04)	9 (4.11)	15 (12.30)		
Focal epilepsy syndrome	155 (45.45)	111 (50.68)	44 (36.07)		
Generalized epilepsy syndrome	36 (10.56)	22 (10.05)	14 (11.48)		
Non-syndromic	126 (36.95)	77 (35.16)	49 (40.16)		
Etiology of epilepsy, n (%)				χ^2 = 17.81	**<0.0001**
Genetic	193 (56.60)	130 (59.36)	63 (51.64)		
Structural	15 (4.40)	2 (0.91)	13 (10.66)		
Others	133 (39.00)	87 (39.73)	46 (37.70)		
Abnormal neurological examination or motor deficit, n (%)				χ^2 = 10.13	**0.0014**
No	304 (89.15)	204 (93.15)	100 (81.97)		
Yes	37 (10.85)	15 (6.85)	22 (18.03)		
Intellectual disability, n (%)				χ^2 = 19.09	**<0.0001**
No	277 (81.23)	193 (88.13)	84 (68.85)		
Yes	64 (18.77)	26 (11.87)	38 (31.15)		
EEG at start of ASM tapering, n (%)				χ^2 = 42.00	**<0.0001**
Abnormal	78 (22.87)	26 (11.87)	52 (42.62)		
Normal	263 (77.13)	193 (88.13)	70 (57.38)		
EEG after ASM tapering, n (%)				χ^2 = 114.07	**<0.0001**
Abnormal	129 (37.83)	37 (16.89)	92 (75.41)		
Normal	212 (62.17)	182 (83.11)	30 (24.59)		
ASM, n (%)	453 instances[b]	n = 276	n = 177	χ^2 = 1.01	0.91
VPA	153 (33.77)	95 (34.42)	58 (32.77)		
LEV	127 (28.04)	76 (27.54)	51 (28.81)		
OXC	77 (17.00)	49 (17.75)	28 (15.82)		
BZDs	32 (7.06)	20 (7.25)	12 (6.78)		
Others	64 (14.13)	36 (13.04)	28 (15.82)		

Z: Mann–Whitney test, χ^2: Chi-square test, –: Fisher exact test; M: Median, Q_1: 1st Quartile, Q_3: 3rd Quartile. Note: Statistically significant values are in bold. Abbreviations: ASM, antiseizure medication; EEG, electroencephalogram; DEE, developmental and epileptic encephalopathies; PNDs, progressive neurological deficit syndromes; BZDs, benzodiazepines; LEV, levetiracetam; OXC, oxcarbazepine; VPA, valproic acid. [a]The biological sex of pediatric participants was determined through medical records, which included documentation of chromosomal or anatomical characteristics at birth or during clinical assessments. [b]Validation cohort of 341 individuals included 453 instances of ASM use.

Table 3: **Characteristics of validation cohort.**

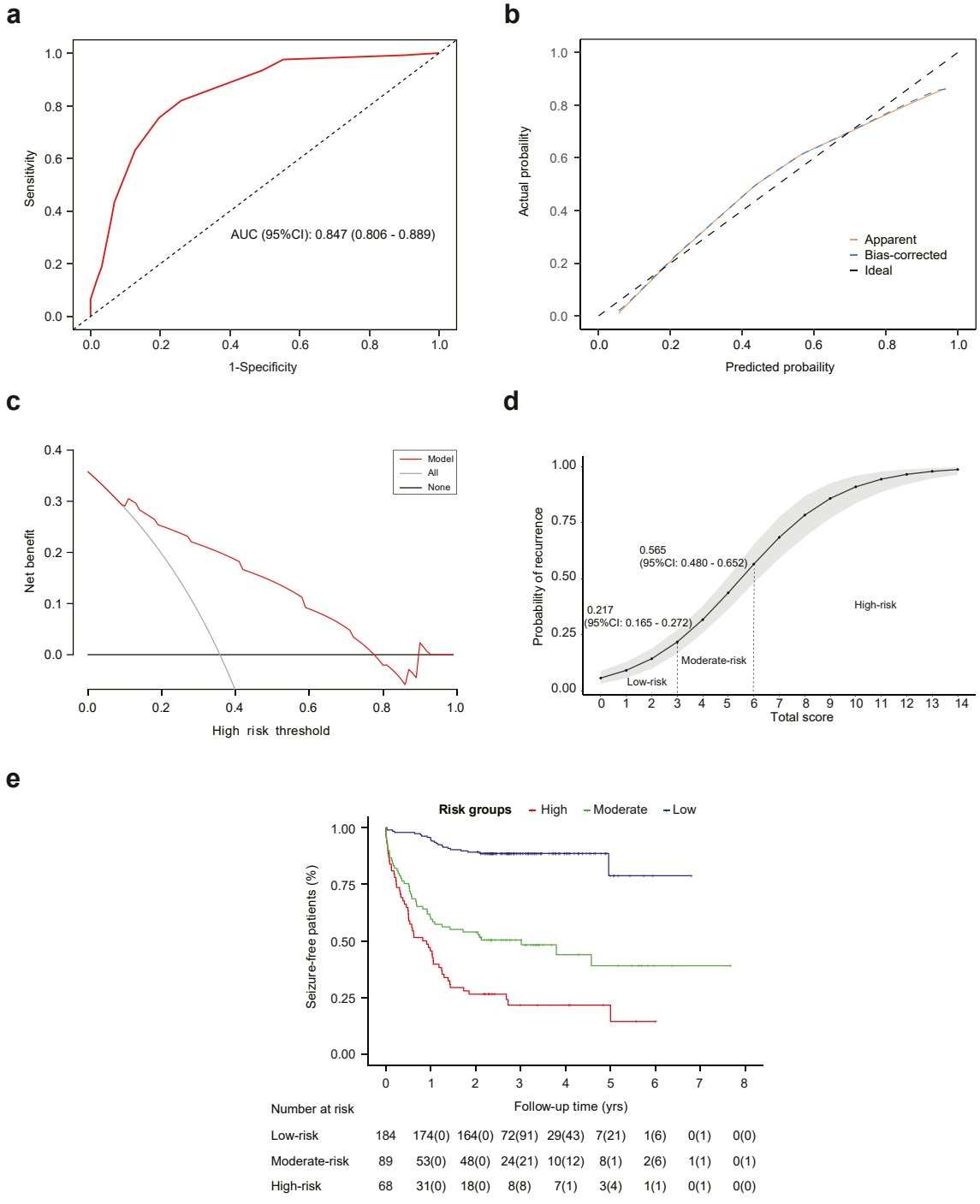

Fig. 4: **Performance and predictive power of seizure recurrence risk predictive model in children with epilepsy**. a: ROC curve for seizure recurrence risk predictive model. b: Calibration curve of the model. c. DCA of the model. d: The corresponding risk percentages associated with each sum score. e: K-M curve of seizure recurrence end point for each risk group in the validation cohort. Numbers at risk (with censored individuals in brackets) are displayed below the plot at each annual interval. Moderate-risk group: RR 4.42 (95% CI: 2.85–6.85), $P < 0.0001$; high-risk group: 6.52 (95% CI: 4.32–9.84), $P < 0.0001$.

post-withdrawal EEG data are unavailable. The simplified scoring system (Table S5) provides a validated alternative for guiding ASM withdrawal decisions in resource-limited settings where serial EEG monitoring is impractical. Moreover, EEG abnormalities alone, without other risk factors should not preclude the

discontinuation of ASMs in seizure-free children, as comprehensive risk stratification (via the scoring system) and clinical judgment remain paramount.

Age at epilepsy onset also emerged as a crucial predictor of recurrence. Intriguingly, younger onset age was associated with a lower probability of relapse, which may be explained by the predominance of self-limited epilepsy syndromes in children under 10 years of age.[12,57] Conversely, a history of febrile seizures was linked to an increased risk of seizure recurrence, likely reflecting the characteristics of subsequent epilepsy types and the limited representation of self-limited epilepsy syndromes with febrile seizure history.[58] Focal onset seizures occurring independently of a defined epilepsy syndrome are indicative of potential underlying brain lesions.[59] These children are at a higher risk of developing resistance to ASMs and experiencing relapse following the cessation of ASM treatment.[60] Similarly, the presence of cognitive, neurological, or motor impairments suggests underlying focal or diffuse brain lesions,[11] further elevating the risk of seizure recurrence.

The duration of epilepsy was included as a risk factor in this analysis, despite not being among the top 10 risk factors identified in the published literature on pediatric epilepsy. Its inclusion is supported by evidence indicating that inadequate response to initial ASM treatment likely reflects refractory epilepsy.[22] Consistent with findings in both adults and children,[11] longer epilepsy duration was negatively correlated with seizure recurrence. These findings emphasize the importance of prescribing ASMs based on a comprehensive evaluation of patients, underlying causes, seizure types, and associated epilepsy syndrome.

In contrast, seizure frequency—frequently cited as a predictor of relapse in adults—did not show a significant association with recurrence in pediatric epilepsy.[61–65] This discrepancy may be due to several factors. First, seizure frequency in children is often under-reported by parents,[66] resulting in unreliable data. Second, frequent seizures before ASM initiation do not necessarily indicate unresponsiveness to ASMs in children. For instance, PRRT2-associated infantile focal onset epilepsy, the most common self-limited infantile epilepsy,[57] often presents with multiple seizures before responding to sodium channel blockers.[67] Additionally, detailed information regarding seizure frequency as reported by parents was unavailable for individuals in the validation cohort, further complicating its assessment as a predictor.

Lamberink et al. demonstrated that a longer seizure-free interval before ASM withdrawal was negatively associated with seizure recurrence.[11] However, this variable was excluded from our prediction model due to its lack of statistical significance in the meta-analysis. The relatively weak predictive value of seizure-free intervals in pediatric populations, compared to general epilepsy cohorts,[11] may be attributed to several factors, including high heterogeneity in study designs and potential shifts in seizure patterns over time. Furthermore, self-limited epilepsy was not included in our prediction model as it did not rank among the top 10 variables based on our study design. Currently, there is limited data addressing ASM withdrawal in specific electroclinical syndromes,[10] particularly those encompassing broader age ranges, such as self-limited epilepsy with centrotemporal spikes. The higher AUC achieved in this pediatric-specific model compared to study including general populations[11] further highlights the importance of developing age-stratified prediction algorithms. Based on current evidence,[10,32,44,45] maintaining a minimum two-year seizure-free period prior to ASM tapering in children with epilepsy is clinically advisable, as this duration may be associated with a reduced risk of seizure recurrence. Additionally, the algorithm for ASM discontinuation in specific epilepsy syndromes requires further systematic exploration to optimize strategies for reducing seizure relapse.

This study conducted a comprehensive analysis of risk factors identified across 29 initially eligible articles, resulting in over 30 distinct risk factors. To ensure broad clinical utility, it was essential to include a broad spectrum of clinically relevant and readily accessible risk factors.[68] The final prediction model incorporated eight factors derived from the meta-analysis and one clinically relevant factor. In the validation cohorts, VIFs for all predictors demonstrated acceptable collinearity levels, thereby indirectly supporting the independence of these predictive variables. A predictive model is considered robust when the ROC curve yields an AUC value exceeding 0.7.[69,70] During model construction, it was observed that most individual AUC values for the included risk factors were lower than 0.7, except for the post-discontinuation EEG. Therefore, to enhance predictive accuracy, all identifiable factors were combined, allowing for a more precise and comprehensive risk assessment. This is particularly important in resource-limited regions where routine EEG monitoring during ASM withdrawal may not be readily accessible.[71] Importantly, comparative analysis of the four models revealed that the model excluding all EEG findings throughout the ASM tapering process demonstrated the lowest AUC value of 0.694. Notably, this value still indicates clinically acceptable predictive performance, suggesting that the model maintains utility even in settings where EEG monitoring is unavailable. It is important to note that the predictive model only offers statistical probabilities for seizure relapse on an individual basis. These probabilities must be considered alongside other significant factors, such as the social stigma associated with seizures, impact of seizure-related anxiety on daily life, and challenges in accessing medical care in the event of recurrence. Discussions with patients and their guardians should integrate these considerations to guide informed decision-making.

The meta-analytic approach employed to construct this predictive model avoided the need for complex machine learning techniques often required for analyzing unconventional or non-parametric data.[72] Nonetheless, this methodology inevitably introduces several limitations. First, due to heterogeneity in study methodologies and reporting, certain risk factors were amalgamated through subgroup analysis. For instance, in the final model, the age at epilepsy onset was dichotomized using a cutoff of 10 years, improving clinical applicability but potentially obscuring nuanced relationships between variables.[73] Additionally, the predictive model did not provide dynamic predictions for seizure recurrence over time, limiting its ability to account for temporal changes in risk, such as shifts in seizure type, EEG findings, or ASM adjustments during follow-up. Future studies should use longitudinal data to evaluate how predictive accuracy changes over time and identify factors influencing this decline, ultimately improving the model's long-term robustness. Secondly, for studies lacking direct RR reporting, RRs and 95% CIs were approximated using raw frequency data or extracted from figures, which may introduce potential measurement errors. Thirdly, the generalizability of our findings may be constrained by the lack of gender identity data and limited ethnic diversity (predominantly Han Chinese). These factors could influence outcomes in sociocultural contexts where gender-related dynamics (e.g., care-seeking behaviors) or socioeconomic disparities (e.g., healthcare access) modulate epilepsy management. Validation in multiethnic cohorts with integrated gender dimensions is warranted. Finally, while the risk stratification approach, incorporating predictors derived from an analysis of 4080 cases, demonstrated significant discriminative validity through Kaplan–Meier analysis in the validation cohort, the generalizability of these predictive thresholds requires further external validation across diverse clinical settings and pediatric populations, which is crucial for establishing its broader clinical applicability, reliability, and utility across different healthcare contexts.

In conclusion, this study established a predictive model with high performance, that was specifically designed to evaluate the risk of seizure relapse in children with epilepsy during ASM discontinuation. Overall, this predictive model provides a valuable tool to support clinicians and patients in making individualized decisions regarding ASM withdrawal for those who have maintained seizure freedom for at least two years.

Contributors

K.D. conceptualized and designed the study, conducted literature searches and data extraction, collected and validated data, analysed data, and drafted the manuscript. D.T. was responsible for data extraction, cohort follow-up, and data collection. L.B., W.Y., and S.L. were in charge of cohort follow-up and data collection. S.J.L., N.C., and A.S. provided guidance on statistical analysis methods for the article. T.L. conceived and designed the study, drafted the manuscript, and critically reviewed the intellectual content of the article. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication. All authors revised the manuscript and approved the final manuscript as submitted. K.D., D.T., and T.L. accessed and verified the data. All authors are responsible for the decision to submit the manuscript.

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author upon reasonable request for 10 years following the formal publication of this article.

Declaration of interests

All coauthors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103154.

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