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CRITICAL REVIEW

Clinical prediction models for treatment outcomes in newly diagnosed epilepsy: A systematic review

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Abstract

Up to 35% of individuals diagnosed with epilepsy continue to have seizures despite treatment, commonly referred to as drug-resistant epilepsy. Uncontrolled seizures can directly, or indirectly, negatively impact an individual's quality of life. To inform clinical management and life decisions, it is important to be able to predict the likelihood of seizure control. Those likely to achieve seizure control will be able to return sooner to their usual work and leisure activities and require less follow-up, whereas those with a poor prognosis will need more frequent clinical attendance and earlier consideration of epilepsy surgery. This is a systematic review aimed at identifying demographic, clinical, physiological (e.g., electroencephalographic), and imaging (e.g., magnetic resonance imaging) factors that may be predictive of treatment outcomes in patients with newly diagnosed epilepsy (NDE). MEDLINE and Embase were searched for prediction models of treatment outcomes in patients with NDE. Study characteristics were extracted and subjected to assessment of risk of bias (and applicability concerns) using the PROBAST (Prediction Model Risk of Bias Assessment Tool) tool. Baseline variables associated with treatment outcomes are reported as prognostic factors. After screening, 48 models were identified in 32 studies, which generally scored low for concerns of applicability, but universally scored high for susceptibility to bias. Outcomes reported fit broadly into four categories: drug resistance, short-term treatment response, seizure remission, and mortality. Prognostic factors were also heterogenous, but the predictors that were commonly significantly associated with outcomes were those related to seizure characteristics/types, epilepsy history, and age at onset. Antiseizure medication response was often included as a baseline variable, potentially obscuring other factor relationships at baseline. Currently, outcome prediction models for NDE demonstrate a high risk of bias. Model development could be improved with a stronger adherence to recommended TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) practices. Furthermore, we outline actionable

changes to common practices that are intended to improve the overall quality of prediction model development in NDE.

KEYWORDS
intractability, newly diagnosed epilepsy, outcomes, prognosis, seizures, treatment

1 | INTRODUCTION

1.1 | Rationale

1.1.1 | Clinical overview of epilepsy

As one of the most common neurological diseases, epilepsy is estimated to affect more than 70 million people globally.[1,2] Epilepsy incidence tends to be higher in the youngest and oldest age groups, in males, and in low–middle-income countries.[3] Epilepsy is characterized by a predisposition to unprovoked seizure activity, which is thought to arise due to abnormalities within cortical networks.[4–7] The epilepsies are a broad group of syndromes, classified by the International League Against Epilepsy (ILAE), that differ in etiology, seizure type, clinical course, prognosis, and comorbidities.[8,9] An accurate diagnosis is crucial for determining the appropriate first-line treatment, which will most commonly be antiseizure medication (ASM) monotherapy. Alongside seizure activity, people with epilepsy (PWE) are vulnerable to cognitive, behavioral, and neurological comorbidities, as well as diminished education, employment, and relationship opportunities, all of which negatively impact on quality of life. In a recent large-cohort newly diagnosed epilepsy (NDE) study, the rate of 1-year remission (cessation of seizure activity) following ASM mono/polytherapy was 63.7%, and the rate of drug resistance (failure of two or more appropriate ASM trials to control seizure activity) was 36.3%, in line with similar studies.[10–12]

1.1.2 | Drug resistance

The factors underlying drug resistance are unclear, but it has been hypothesized that repeated ictogenic activity is conducive to the development of a more robust epileptogenic network. However, evidence for this in human epilepsy is scant. Although patients with more frequent seizures or higher seizure density before starting treatment have a worse prognosis for seizure control, this most likely represents greater disease severity from the outset. The MESS study showed that administration of ASM immediately following a first unprovoked seizure or early epilepsy resulted in a lower risk of seizure recurrence but had no impact on longer term seizure remission rates.[13] Whether this is a contributing factor in chronic epilepsy remains unclear.

Key points

- This paper presents a systematic literature review of treatment outcome prediction models in NDE.
- The risk of bias in the included models was evaluated using the PROBAST framework, finding a universally high risk level.
- The relationship between seizure characteristics/types, epilepsy history, and age at onset with seizure remission should be examined in future prediction model studies.
- Despite clinical relevance, electrophysiological and MRI findings are underrepresented in multivariable models for treatment outcomes in NDE.
- To improve the overall quality of prediction model development in NDE, prospective authors are advised to adhere to TRIPOD guidelines, and to avoid including response to treatment as a baseline variable.

1.1.3 | Newly diagnosed epilepsy

To better characterize the course of epilepsy and its underlying pathomechanisms, it has been suggested that people with NDE be studied as a distinct group.[14,15] Studying epilepsy at its earliest time point avoids the confounds inherent in studying long-standing epilepsy, including the chronic effects of seizure activity and ASM use; seizure activity in chronic epilepsy can cause injuries and might encourage the development of drug resistance in PWE, and successive ASM regimens are associated with a reduction in the chance of attaining seizure freedom.[16–19] To reliably model epilepsy outcomes at diagnosis, predictive models should be developed using data collected prospectively from NDE cases, thus

avoiding the assumption that the trajectory of epilepsy is linear and constant, or the need to control for events that may have occurred since diagnosis.

1.1.4 | Treatment outcomes

Early seizure control has been indicated to be crucial for ensuring optimal quality of life outcomes in NDE, putatively due to the prevention of further disruptions to seizure-related functional networks.[5,20–23] Epilepsy treatment is individualized to ensure that (1) the risk–benefit ratio of a proposed therapy is suitable and (2) the patient with epilepsy is receiving the most efficacious treatment.[24] The decision to begin a particular regimen is made after the consideration of several potential contraindications, such as pregnancy, medical interactions, and the risk of adverse effects.[25] Importantly, the treatment choice will also be informed by the likelihood of achieving seizure freedom on a particular ASM (the efficacy) and the proportion of PWE who persist with the drug trial (the effectiveness). Predicting treatment outcomes—such as seizure remission, refractoriness, and drug resistance—is nontrivial, also requiring the consideration of factors like age at onset (and the related epilepsy duration), the number of pretreatment seizures, electroencephalographic (EEG)/imaging abnormalities, intellectual impairments, etiology, and seizure characteristics to inform trajectories.[26–29]

1.1.5 | Prediction models

Prediction models are combinations of prognostic factors used to estimate the risk of a specific endpoint. Built with and validated on large cohorts, prediction models allow for individual patient outcomes to be estimated according to a formal statistical framework.[30] Prognostic and diagnostic models are commonplace in epilepsy care, and the principal benefit of multivariable models (over the use of univariable factors for prediction) is accuracy, especially considering the complexity of epileptic processes.[31,32] Single biomarkers (quantifiable properties indicative of normal biological processes) in epilepsy are thought to lack the granularity and robustness necessary to allow for clinical application.[33] For example, several studies have investigated the relationship between EEG abnormalities and outcomes, often providing conflicting or incongruous evidence; although it is probable that some association exists, it is likely that EEG patterns and features influence/are mediated by external factors, and further multivariable research is required to determine how.[34] To facilitate application and future evaluation (as in with systematic reviews) it is recommended that prediction models be designed and reported in a systematic manner, such as is outlined by Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[35] Adherence to a predefined set of guidelines, such as TRIPOD, helps to ensure that the risk of bias (RoB; systematic error) and amount of applicability concerns in the resultant study are kept to a minimum.[36] Several models for the prediction of treatment outcomes in NDE have already been proposed, the latest systematic review of which was published in 2014.[37,38]

1.2 | Objectives

The aim of this systematic review is to summarize the findings and evaluate the bias of currently available multivariable prediction models of treatment outcomes in NDE. As new prediction models are developed and validated, it is crucial that they be presented in a format that allows for optimal dissemination of their actionable conclusions. Furthermore, information from previous reviews may be outdated and misleading in the context of more recent findings. The most recent comparable review, carried out by Abimbola et al. in 2014, presents several opportunities for improvement (besides being updated), namely that only studies with samples of >100 were included and no evaluation of RoB was carried out.[37] A systematic examination of multivariable prediction models for treatment outcomes in NDE was undertaken here to provide an updated and expanded review of the state of the literature, and to facilitate understanding of their conclusions. All included models were evaluated for RoB and applicability concerns using the Prediction Model Risk of Bias Assessment Tool (PROBAST) framework.[36] Between the models, common prognostic factors were identified and are presented herein, with the intention of informing future prediction model studies in NDE.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

This review is reported in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and a non-peer-reviewed, publicly available protocol was registered with PROSPERO (ID: CRD42022329936).[39]

2.2 | Eligibility criteria, information sources, search, study selection, and data collection process

MEDLINE and Embase were searched for relevant publications, using PubMed/MeSH (Medical Subject Headings) and Scopus/Boolean terms, respectively. Full queries can be seen in Appendix A. Data were screened by C.R. and L.J.B. independently, with mediation of any conflicting exclusions following consensus meetings provided by S.S.K. Studies were included if they contained a multivariable model of treatment outcomes in a discrete sample of NDE, meeting the following criteria:

- Study design: Any primary design including (but not limited to) cohort studies (retrospective, prospective, hybrid), randomized control trials, quasirandomized control trials, observational studies, and case–control studies.
- Participants: Any person with NDE defined using the operational ILAE definition of two clinically unprovoked seizures, or one unprovoked seizure with a >60% probability of recurrence (other definitions were evaluated for agreement with the ILAE definition ad hoc).[40] Provoked seizures include those deemed situational or due to acute neurological insult/precipitant.[41]
  - A sample was considered to meet the criteria for "newly diagnosed" epilepsy if reported as such in the study and/or no evidence suggesting that participants in the sample were recruited >12 months after their diagnosis or had previously undergone surgical intervention for epilepsy was presented.[14] To include as many clinically relevant studies as possible, ASM use was not an exclusion criterion. Furthermore, any adverse effects at the time of recruitment were expected to be minimal.[17]
- Multivariable model: Prediction models, developed with at least two demographic, clinical, neuroimaging, and/or electrophysiological factors collected and assessed as part of standard clinical practice at baseline upon a new diagnosis of epilepsy, that are associated with 12 months of continuous seizure freedom (remission). Demographic factors are socioeconomic attributes that can be statistically expressed—for example, age, sex, and education level. Clinical factors are signs and symptoms of disease classification or severity including etiology, type and frequency of seizure, age at onset of epilepsy, and duration of illness prior to diagnosis. The neuroimaging and neurophysiological factors include assessments of standard magnetic resonance imaging (MRI) and EEG examinations, respectively, often taken upon a new diagnosis of epilepsy.
  - Our search terms were not designed to capture studies that made use of machine learning (ML)/deep learning, due to the complexities introduced by the structure of these models, which are not often compatible with those of typical regression-based models.[42,43]
- Primary outcomes: Twelve months (or longer) of continuous seizure freedom (remission). The time frame of 12 months was chosen in accordance with previous literature suggesting that as one seizure per year is sufficient to preclude PWE from driving, seizure freedom should be measured over the same time frame.[11] Furthermore, after 12 months of treatment, if seizures are not controlled it has been recommended that PWE be referred to a specialist clinic.[44]
- Secondary outcomes: Reported seizure remission of any duration at any time point; treatment failure (adverse effects, intractability, etc.) reported in any form and at any time.

Model and outcome data extraction was carried out on the whole sample by C.R. and V.P. independently, using a predefined form to ensure that all relevant information was extracted systematically.

2.3 | RoB in individual studies

RoB was determined on a per-study basis, using 20 signaling questions over four domains (Participants, Predictors, Outcomes, Analysis); the answers to the questions indicate potential for bias, which then informs the (semisubjective) potential for bias in that domain. If any domain is flagged as having a high potential for bias, the study is judged to have a high overall RoB.[45] Similarly, three of the four domains contain an applicability concerns judgment, whereby the rater evaluates to what extent the study content matches the research question. High concern for applicability in any domain results in the study also receiving a high applicability concern rating.[36] Data required for RoB and applicability concern assessment were also extracted by C.R. and V.P., who independently evaluated all 32 studies in the sample.

2.4 | Summary measures, synthesis of results, RoB across studies, and additional analyses

Data pertinent to describing the setting, methodology, demographics, predictors, and outcomes for individual studies was synthesized into narrative form and evidence tables. Metadata for quality assessment purposes were also extracted. Sankey plots were constructed to visually present the distribution of outcomes across studies and

predictors across outcomes. Definitions for the categories proposed in this study can be found in Appendix B.

3 | RESULTS

3.1 | Study selection

After the removal of 285 duplicate entries, 878 records were excluded first based on their titles, then abstracts (for a PRISMA diagram, see Figure 1). The remaining 128 reports were sought for retrieval, of which 126 were obtained. The retrieved reports were then assessed for eligibility, during which 77 were excluded due to univariable modeling ($n = 44$), unsuitable cohorts ($n = 20$), unsuitable outcomes ($n = 12$), or absence of primary analysis ($n = 1$). The remaining reports underwent data extraction, during which 17 were deemed ineligible.[46]

3.2 | Study characteristics

After screening, 32 studies were deemed suitable for inclusion (Figure 1), including 48 models. Twelve studies used prospectively recruited PWE (37.5%), 17 used retrospective data (53.1%), and three used a combination

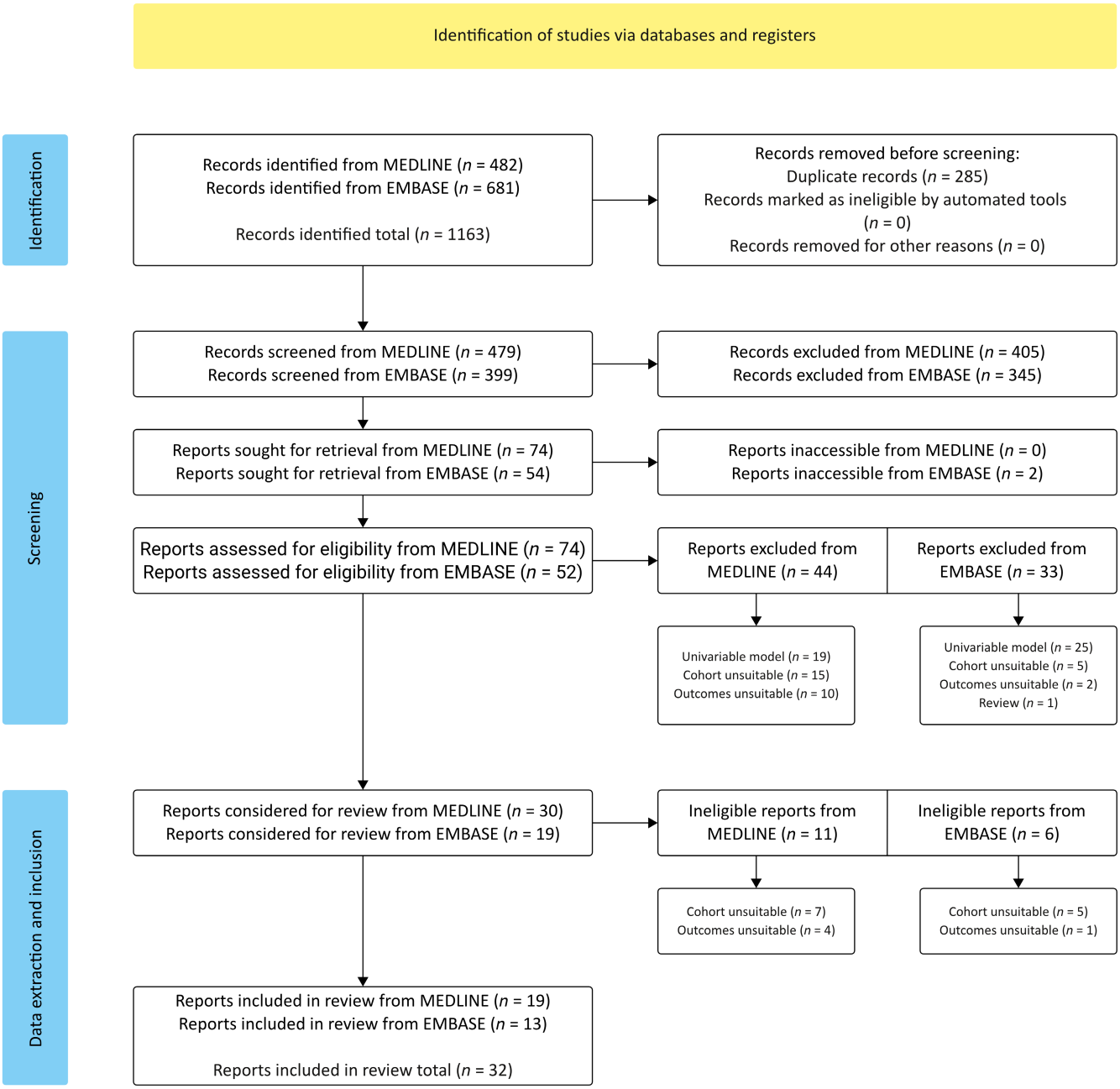

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection.

(9.4%). Designs included one case–control study, two randomized control trials, and 29 cohort studies. Sample sizes ranged from 53 to 99 990 PWE, with a median value of 261. Estimates of "events per variable" ranged from .63 to 3927.38, with a median value of 9.86 (for study characteristics, see Table 1). Of 32 studies, 12 utilized Cox proportional hazards models (37.5%), whereas the remaining 20 employed logistic regressions (62.5%) to build their prediction models. Outcomes were evaluated at time points that ranged from 16–20 weeks, up to 32–36 years, with several studies assessing outcomes at the arbitrary date of the last follow-up. Of the included studies, 19 did not report a sample restricted to any specific epilepsy diagnosis. Of the remaining 13, seven investigated focal epilepsy, and six investigated generalized epilepsy. There was a large amount of variation in the ages of the included participants; the samples for 13 studies were selected from a "childhood" population (<16 years of age), six from an "adult" population (16–65 years), four from a "senior" population (>65 years), and nine from any mixture of the other three.

Across all models, 41 unique outcomes were operationalized, which were subsequently stratified into four categories: Mortality, Drug Resistance, Seizure Remission, and Short-Term Treatment Response, as shown in Figure 2 (a complete list of outcomes is provided in Appendix C). In accordance with the review objectives, the seizure remission category was used for seizure outcomes of 12 months or longer, with all seizure outcomes of >12 months being categorized as short-term treatment response. Sixty-nine unique predictors were operationalized, which were subsequently stratified into 11 categories: Age, ASM, Comorbidity, Demographics, Diagnosis, EEG, History, Neuroimaging, Neuropsychology, Response, and Seizure Characteristics/Types (a complete list of predictors is also provided in Appendix C, with a Sankey diagram illustrating the flow of outcomes, predictors, and predictor categories from each study in Appendix D). Although unavailable at baseline, response (to treatment) variables were recorded in a number of studies and contributed significant predictors to several multivariable prediction models.

3.3 | Results of individual studies

In the included studies, there were 40 cases of variables being statistically significant as predictors of seizure remission, of which 13 were categorized as response variables and 11 were seizure characteristics (Table 2). Across all included models, 112 relationships between predictors and outcomes were found to be statistically significant, with variables from the seizure characteristics category being reported as significant most frequently (35 significant relationships). Response variables were the next most frequent, with 16 significant relationships, followed by history and comorbidity (10 each). Outcomes were most commonly categorized as short-term treatment response, followed by seizure remission, drug resistance, and then mortality.

Research trends were explored by stratifying the studies by sample age and diagnosis. The significance of seizure characteristics was consistent across studies regardless of diagnosis (i.e., focal, generalized, or nonspecific); however, neuroimaging variables were prevalent in the final models of focal epilepsy studies and ASM-related variables were prevalent in models of generalized epilepsy studies, whereas comorbidities and demographics appeared to be more strongly associated with nonspecific epilepsy cohorts. When the studies were stratified by age group, treatment outcomes in senior populations were associated with demographic variables. Alongside seizure characteristics, the childhood epilepsy studies predominantly reported significant age- and ASM-related variables, the adult epilepsy studies reported diagnostic and neuroimaging predictors, and variables relating to comorbidity and history were prevalent in the mixed-age strata.

3.4 | RoB within studies

After PROBAST assessment had reached consensus, nine (28.1%) studies ranked highly for applicability concerns, whereas all 32 studies demonstrated a high RoB (Table 3). Applicability concerns for the participant domain were all low, but high for eight studies in the predictor domain, which was related to the inclusion of response to treatment as a prognostic factor. Applicability concern levels were also high for two studies in the outcome domain.[36] RoB was generally low in the participant domain, but universally high in the predictor, outcome, and analysis domains.

4 | DISCUSSION

4.1 | Summary of evidence

4.1.1 | Review summary

The authors systematically identified 32 studies that used multivariable prediction models to assess the

TABLE 1 Summary of included studies.

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Model predictors
Aikiä et al., 1999	89	Partial epilepsy	Group 1 [*n* = 79]: 34.40 (15.30) Group 2 [*n* = 10]: 29.20 (12.40)	Refractory seizure disorder	2 years	Logistic regression	Age at diagnosis (younger = greater likelihood of poor 2-year outcome) Etiology (remote symptomatic = greater likelihood of poor 2-year outcome) Seizure type (partial complex or mixed = greater likelihood of poor 2-year outcome) Spike focus (presence = greater likelihood of poor 2-year outcome) Immediate list recall (impairment = greater likelihood of poor 2-year outcome) Delayed list recognition (impairment = greater likelihood of poor 2-year outcome)
Arya et al., 2016	445 445	Childhood absence epilepsy	7.42 (2.58–12.92)[a]	Freedom from failure Seizure freedom	16–20 weeks 16–20 weeks	Logistic regression	ASM (LTG = reduced chance of freedom from failure) ASM (LTG = reduced chance of seizure freedom) BMI (ns)
Ashmawi et al., 2016	287 287	NS	15.60 (11.50)	2-year remission 2-year sustained remission	4–20 years 4–20 years	Cox proportional hazards	Nocturnal seizures (yes = reduced chance of sustained 2-year remission) First ASM response (bad = reduced chance of 2-year remission) First ASM response (bad = reduced chance of 2-year sustained remission) Family history of epilepsy (ns) Neuroimaging (ns) Neurological evaluation (ns) Pretreatment seizure number (ns) Seizure types (ns) Etiology (ns)
Beydoun et al., 2015	234	Focal epilepsy	31.60 (21.90)	6-month terminal seizure remission at month 12	1 year	Cox proportional hazards	Epileptogenic lesion on neuroimaging (yes = less likely to experience 6-month terminal remission at month 12) Baseline seizure type (simple partial = less likely to experience 6-month terminal remission at month 12) Age (ns) Sex (ns)
Blank et al., 2021	99 990	NS	>65.00	5-year mortality	5 years	Cox regression	Sex (female = decreased risk of mortality) Race (Asian = decreased risk of mortality) Ethnicity (Hispanic = decreased risk of mortality) Comorbidity (yes = increased risk of mortality) Medicaid coinsurance (yes = increased risk of mortality) Rural–urban continuum code (intermediate = increased risk of mortality)

(Continues)

TABLE 1 (Continued)

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Model predictors
Bruun et al., 2016	293 293	NS	>65.00	2-year remission 5-year seizure remission	2–5 years 5 years	Cox proportional hazards	Seizure remission within the first year of ASM treatment (no = less likely to attain 2-year remission) Sex (ns) Age at diagnosis (ns) Etiology (ns) Pretreatment EEG (ns) Seizure type (ns) Number of seizure types (ns) Pretreatment seizure number (ns) Pretreatment time (ns)
Cerulli Irelli et al., 2022	113 113	Juvenile myoclonic epilepsy	14.00 (10.00–16.00)[a]	4-year seizure remission Delayed sustained remission	9.50–27 years 9.50–27 years	Multinomial logistic regression	Absence seizures (present = lower remission probability) Age at onset (earlier = remission delay) Catamenial seizures (present = remission delay) Photosensitivity (ns) Myoclonic status epilepticus (ns) Focal EEG asymmetries (ns)
Chen et al., 2017	1795	NS	33.00 (9.00–93.00)[a]	Terminal seizure outcome	2–12 years	Cox proportional hazards	Age at onset (<5 = lower likelihood of treatment response) Attack frequency (higher = lower likelihood of treatment response)
Chen et al., 2021	106	Benign epilepsy	7.15 (1.82)	Treatment response	1 year	Logistic regression	Seizures in the year prior to treatment (more = poorer chance of seizure freedom) Recreational drug use (yes = poorer chance of seizure freedom) Family history of epilepsy (more = poorer chance of seizure freedom)
Dlugos and Buono, 2004	129	Focal epilepsy of presumed temporal lobe origin	Trial failure: 6.20 (4.00) Seizure free: 7.70 (3.90)	CBZ trial failure	1 year	Logistic regression	Early risk factor for epilepsy (yes = higher chance of trial failure) Temporal neuroimaging abnormality (yes = higher chance of trial failure)
Dlugos et al., 2013	329 329	Childhood absence epilepsy	NS (2.58–12.92)[a]	Freedom from failure at 16–20 weeks Seizure freedom at 16–20 weeks	16–20 weeks 16–20 weeks	Logistic regression	ASM (ETX over LTG = greater chance of freedom from failure) Shortest seizure duration (longer = greater chance of freedom from failure) ASM (ETX over LTG = greater chance of seizure freedom) Shortest seizure duration (longer = greater chance of seizure freedom) Age (ns) VPA vs. ETX (ns) Occipital intermittent rhythmic delta activity (ns) Focal sharp waves (ns)

TABLE 1 (Continued)

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Model predictors
Dragoumi et al., 2013	303 303 303 303 303	Idiopathic childhood epilepsy	6.70 (3.00)	12-month remission at 2 years Occurrence of seizures in the initial 12 months Occurrence of seizures in the preceding 2 years at 4 years Occurrence of seizures in the preceding 2 years at study end Remission–relapse pattern	2 years 1 year 4 years <22 years <22 years	Logistic regression	Diagnosis (CAE = increased chance of remission at 2 years) Response (early = increased chance of remission at 2 years) Age at onset (older = decreased chance of seizure occurrence in the first 12 months) Academic performance (high = decreased chance of seizure occurrence in the preceding 2 years at 4 years) Age at onset (older = decreased chance pattern C) Response (early = decreased chance pattern C) Response (immediate = decreased chance pattern C) Status epilepticus (yes = increased chance of seizure occurrence in the first 12 months) Multiple seizure types (more = increased chance of seizure occurrence in the first 12 months) History of febrile seizures (yes = increased chance of seizure occurrence in the preceding 2 years at 4 years) History of migraine (yes = increased chance of seizure occurrence in the preceding 2 years at 4 years) Multiple seizure types (more = increased chance of seizure occurrence in the preceding 2 years at study end) Early response (no = increased chance of seizure occurrence in the preceding 2 years at study end) History of migraine (yes = increased chance of seizure occurrence in the preceding 2 years at study end) Initial response to treatment (no = increased chance of seizure occurrence in the preceding 2 years at study end) Multiple seizure types (more = increased chance of pattern C) History of migraine (yes = increased chance of pattern C)
Gasparini et al., 2013	186	Cryptogenic focal epilepsy	39.00 (22.00)	5-year seizure remission	5–21 years	Cox proportional hazards	Family history (epilepsy or febrile seizures = increased chance of remission) Lobe localization (front = increased chance of remission)
Gidey et al., 2020	404	NS	27.40 (11.20)	Seizure recurrence	2–7 years	Cox proportional hazards	Pretreatment seizure number (greater = decreased chance of achieving seizure remission) Treatment adherence (poor = decreased chance of achieving seizure remission)

(Continues)

TABLE 1 (Continued)

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Model predictors
Hersi et al., 2021	459	NS	45.00 (31.00)[b]	12-month seizure freedom	1–11 years	Binary logistic regression	Sex (male = more likely to achieve remission) Etiology (unknown = more likely to achieve remission) EEG (epileptiform activity = less likely to achieve seizure freedom) Age at diagnosis (ns) First ASM choice (ns) First seizure type (ns)
Hitiris et al., 2007	780	NS	31.00 (9.00–93.00)	Seizure-free for past 12 months	2.50–21 years	Binary logistic regression	Family history of epilepsy (yes = greater risk of drug resistance) History of febrile seizures (yes = greater risk of drug resistance) Traumatic brain injury (yes = greater risk of drug resistance) Psychiatric comorbidity (yes = greater risk of drug resistance) Recreational drug use (yes = greater risk of drug resistance) More than 10 seizures before treatment (yes = greater risk of drug resistance) Sex (ns) Neurological deficit (ns) Mental retardation (ns) Seizures for >1 year pretreatment (ns)
Huang et al., 2016	298	NS	70.50 (10.10)	50% seizure reduction	2 years	Logistic regression	Age at onset (older = more likely to achieve satisfactory seizure control at 2 years) ASM treatment (yes = more likely to achieve satisfactory seizure control at 2 years)
Jiang et al., 2017	336 336	NS	11.00 (10.00)[b]	2-year remission at short-term follow-up 5-year remission at long-term follow-up	5 years 5–8 years	Logistic regression	Time to treatment (>12 months = more likely to experience unfavorable short-term outcomes) Seizure frequency in the first year of treatment (>2 = more likely to experience unfavorable short-term outcomes) Seizure frequency in the first year of treatment (>2 = more likely to experience unfavorable long-term outcomes) Sex (ns) Age at onset (ns) Pretreatment seizure density (ns) Multiple seizure types (ns) Status epilepticus (ns) Etiology (ns) EEG (ns) Neuroimaging (ns)

TABLE 1 (Continued)

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Model predictors
Kessler et al., 2017	310	Childhood absence epilepsy	NS (2.58–12.92)[a]	Seizure freedom at 16–20 weeks	16–20 weeks	Logistic regression	Shortest burst duration on baseline EEG (short = higher chance of seizure freedom) LTG vs. ETX (LTG = lower chance of seizure freedom) Cluster pattern 2 (yes = lower chance of seizure freedom) Cluster pattern 2/4 (yes = lower chance of seizure freedom)
Kim et al., 2017	53	Focal epilepsy	35.60 (15.80)	<6 months of continuous seizure freedom	>1 year	Logistic regression	Corpus callosum volume (lower = good ASM response) Age at onset (ns) Prediagnostic duration (ns) Pretreatment seizure frequency (ns)
Kwong et al., 2007	121	NS	5.71 (4.58)	Seizure freedom	1.08–3 years	Forward logistic regression	Acute seizure-related hospitalizations (yes = more likely not to achieve seizure freedom) Age at onset (ns) Seizure frequency at onset (ns) No initial ASM (ns) Initial seizure type (ns) Syndrome (ns) Etiology (ns) Neurodevelopmental status (ns) Status epilepticus (ns) History of neonatal seizure (ns) History of febrile seizure (ns) Not on ASM at time of seizure-related hospitalization/within 3 months of diagnosis (ns) Subtherapeutic ASM dose at time of seizure-related hospitalization/within 3 months of diagnosis (ns)
Li et al., 2021	472	NS	18.90 (14.00)	3-year seizure freedom	>3 years	Logistic regression	Seizure types (multiple = greater chance of poor drug response) Polytherapy (yes = greater chance of poor drug response) History of perinatal injury (ns)
Mangunatmadja et al., 2021	71	Focal epilepsy	<3.00	Intractable epilepsy	1.08–2.83 years	Forward logistic regression	Seizure-type evolution (generalization at study end = greater chance of intractability) Background rhythm evolution (abnormal at study end = greater chance of intractability)

(Continues)

TABLE 1 (Continued)

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Model predictors
Ollivier et al., 2009	180 156	Childhood absence epilepsy	7.00 (2.94)	Complete disappearance of absence seizures during VPA treatment Long-term seizure freedom	1–9 years 1.08–9 years	Logistic regression	Age at diagnosis (older = protective factor against nonresponsiveness to VPA) Pretreatment seizure frequency > 10/day (yes = risk factor for nonresponsiveness to VPA) Presence of GTCS (yes = risk factor for nonresponsiveness to VPA)
Oskoui et al., 2005	196 196 196 196	NS	7.60 (3.70)	Lower probability of seizure remission at 12 months Lower probability of seizure remission at 3 months Poor outcome at 12 months Poor outcome at 3 months	1 year 3 months 1 year 3 months	Logistic regression	Diagnosis (IGE = decreased chance of poor outcome at 3 months) More than one seizure type (yes = increased chance of intractability at 12 months) Seizure recurrence in the 6–12 months posttreatment (yes = increased chance of intractability at 12 months) Mental retardation (yes = increased chance of intractability at 12 months) More than one seizure type (yes = increased chance of intractability at 3 months) More than one seizure type (yes = increased chance of poor outcome at 12 months) Global developmental delay at onset (yes = increased chance of poor outcome at 12 months) Seizure recurrence in the 6–12 months posttreatment (yes = increased chance of poor outcome at 12 months) More than one seizure type (yes = increased chance of poor outcome) Global developmental delay at onset (yes = increased chance of poor outcome at 3 months)
Park et al., 2014	100	NS	16.00 (1.00–77.00)[a]	Seizure-free for past 6 months	6 months	Logistic regression	Age at onset (16+ = increased chance of being a responder) Pretreatment duration (ns) Pretreatment seizure frequency (ns) Pretreatment seizure density (ns)
Quintana et al., 2021	110	NS	52.60 (19.60)	Mortality	3.25–5.75 years	Cox proportional hazards	Older age (higher = increased risk of mortality) Tumor-related etiology (yes = increased risk of mortality) Generalized seizures (yes = increased risk of mortality)

TABLE 1 (Continued)

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Model predictors
Sharma et al., 2021	598 380	NS	39.00 (14.00–88.00)[a]	12-month seizure remission Seizure recurrence	1–8 years 1–8 years	Cox proportional hazards	Epileptogenic neuroimaging findings (yes = higher rate of seizure recurrence) Prediagnosis seizure number (5+ = higher rate of seizure recurrence; ns for rate of seizure recurrence) Treatment approach (deferred = higher rate of seizure recurrence; ns for remission) Sleep status (ns for rate of seizure recurrence) Sex (ns for 12-month remission) Aboriginal or Torres Strait Islander origin (ns for remission) Epilepsy type (ns for remission) Prediagnosis tonic–clonic seizures (ns for remission) Initial use of second-generation ASM (ns for remission)
Sillanpää and Shinnar, 2002	115	NS	<16.00	5-year terminal remission	32–36 years	Cox proportional hazards	Response (early = increased probability of remission) Seizure type (partial or atonic = decreased probability of remission) Status epilepticus (occurrence = lower rate of remission)
Tartara et al., 2022	162	NS	73.20 (7.20)	Seizure freedom	1–19 years	Cox proportional hazards	Etiology (unknown = lower risk of recurrence) Subjective perceptions at seizure onset (presence = higher risk of recurrence) Leukoaraiosis (presence = higher risk of recurrence) Age at onset (ns) Gender (ns)
Yang et al., 2020	543 543	NS	24.86 (12.88)	Seizure freedom at 12 months Seizure freedom at 6 months	1 year 6 months	Cox proportional hazards	Circadian rhythm (seizures in wake and sleep = poor probability of seizure freedom) Pre-ASM EEG (epileptiform discharges = poor probability of seizure freedom) Neuropsychiatric disorder (presence of any = poor probability of seizure freedom) Perinatal brain injury (yes = poor probability of seizure freedom) History of CNS infection (yes = poor probability of seizure freedom)
Zhang et al., 2013	180	NS	19.00 (6.00–21.00)[a]	Poor outcome	>2 years	Logistic regression	Multiple seizure type (yes = greater chance of poor outcome) Changes in seizure type during treatment (yes = greater chance of poor outcome)

Note: Where available, ages are presented in years as mean (SD). Epilepsy diagnoses are reported as in the original studies.

Abbreviations: ASM, antiseizure medication; BMI, body mass index; CAE, childhood absence epilepsy; CBZ, carbamazepine; CNS, central nervous system; EEG, electroencephalogram; ETX, ethosuximide; GTCS, generalized tonic–clonic seizures; IGE, idiopathic generalized epilepsy; LTG, lamotrigine; ns, not significant; NS, not specified; PWE, people with epilepsy; VPA, valproate.

[a]Median (range).

[b]Median (interquartile range).

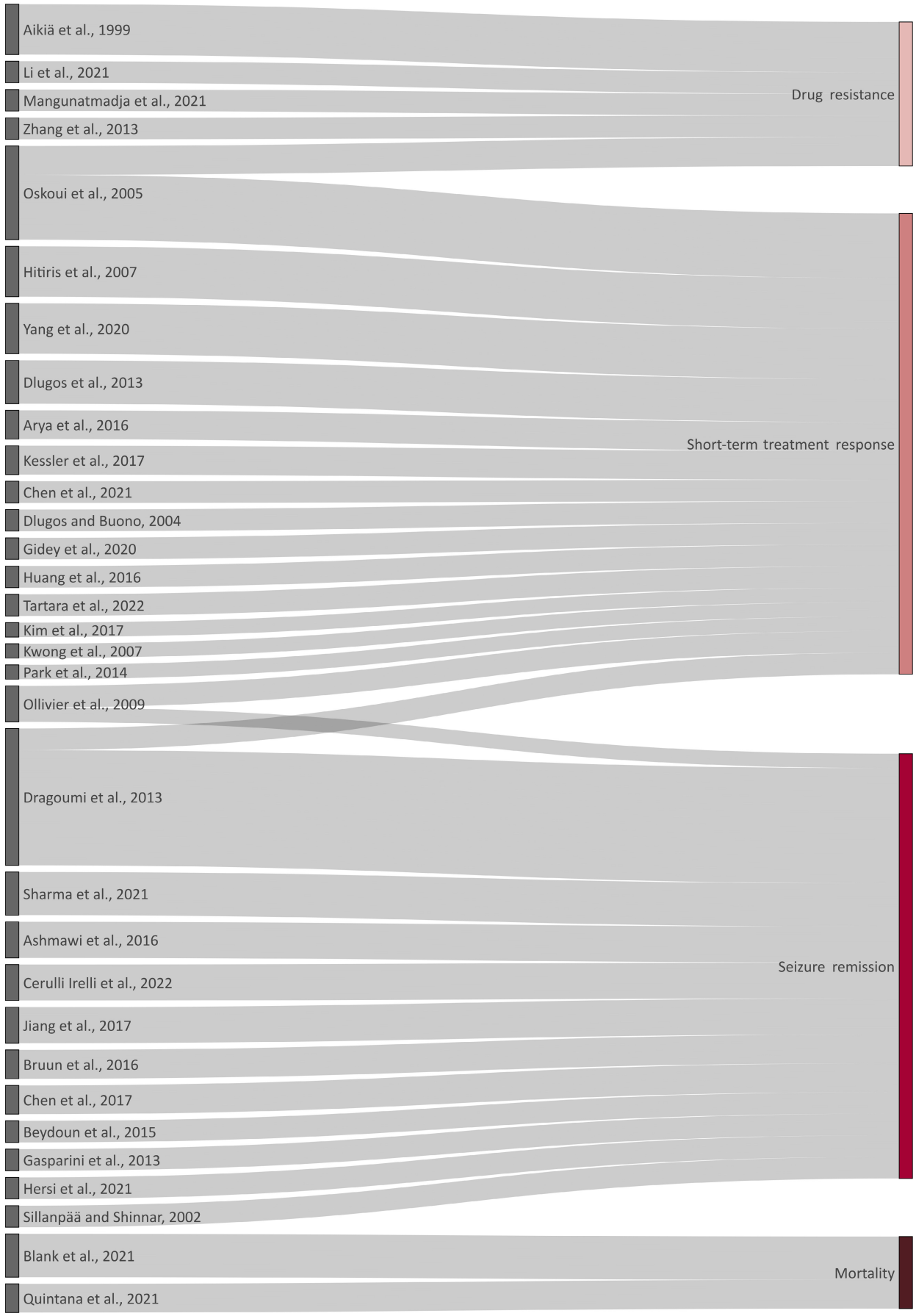

FIGURE 2 Sankey diagram visually illustrating how different outcome categories were represented across studies.[10,26,29,47–75]

TABLE 2 Summary count of predictor instances, sorted by outcome.

Predictor category	Mortality	Drug resistance	Seizure remission	Short-term treatment response	Total
Age	1	1	2	5	9
ASM	0	1	0	6	7
Comorbidity	1	3	1	5	10
Demographics	5	0	1	0	6
Diagnosis	1	1	2	2	6
EEG	0	2	1	2	5
History	0	0	6	4	10
Neuroimaging	0	0	2	5	7
Neuropsychology	0	0	1	0	1
Response	0	1	13	2	16
Seizure characteristics/types	1	6	11	17	35
Total	9	15	40	48	112

Abbreviations: ASM, antiseizure medication; EEG, electroencephalography.

multifactorial prognosis of treatment outcomes in NDE. High RoB was found in all included studies when evaluated with PROBAST. Seizure characteristics/types, epilepsy history, and age at onset were the factor categories most commonly associated with seizure remission. Factors related to comorbidities, demographics, diagnosis, EEG, neuroimaging, and neuropsychology were reported as significantly related to seizure remission either once or twice, whereas ASM-related factors were not. Bias and applicability concern levels were largely influenced by several studies including response to treatment as a baseline variable.

NDE is an area of research importance in the exploration of the pathomechanisms underlying the development of an epileptogenic environment, and aside from integrating recent research, this review expands on previous NDE prediction model reviews in two ways. First, the most recent review by Abimbola et al. in 2014 did not include studies with sample sizes of <100, which this review does.[37] Broadening the inclusion criteria for studies facilitates iteration of the review question over time and encourages the exploration of specific research questions within the same area. Second, quality (in the form of RoB and applicability concern) assessment of the included studies was carried out by two independent reviewers (C.R. and V.P.) in accordance with PROBAST, this being the first review of epilepsy prediction models to do so.[36] To best meet our primary objective—to inform the prognostic factor choices of future prediction model studies—this report has been prepared in accordance with PRISMA (where appropriate), ensuring maximum transparency, reproducibility, and clarity.[46]

4.1.2 | Model descriptives

In the included studies, seizure characteristics and epilepsy history were frequent statistically significant prognostic factors for seizure remission. The predictors and the outcomes of the included studies were heterogenous, so were stratified into categories to aid interpretation. The most common outcome was short-term treatment response, followed by seizure remission, which aligned with our secondary and primary outcomes of interest, respectively. Models of drug resistance and mortality were also reviewed, which address two of the potential treatment failure outcomes. One fifth (20%) of the studies included in this review included treatment response variables as predictors, which limits the applicability of the resultant models. Although statistical significance does not always confer clinical importance, prediction models are at their most informative when being used to inform treatment initiation, that is, at baseline/diagnosis. Unsurprisingly, treatment response was often a statistically significant prognostic factor of treatment outcome and potentially obscured predictive relationships that are interrogatable at baseline, such as treatment decision.

Herein, we also present a summary of the distribution of significant variables across studies when stratified by age and diagnosis. Our findings suggest that either the choice of variables included at baseline is influenced by sample characteristics, treatment outcomes in different age groups and epilepsy syndromes are most accurately predicted by different variables, or more probably, a combination of the two. To better understand from where these imbalances originate, a larger sample of studies is required—not only for statistical power, but also to facilitate more meaningful, distinct, and representative

TABLE 3 Summary of the Prediction Model Risk of Bias Assessment Tool risk of bias and applicability concern assessment of the included studies.

Citation	1.a	1.1	1.2	1.b	2.a	2.1	2.2	2.3	2.b	3.a	3.1	3.2	3.3	3.4
Aikiä et al., 1999	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	NI	Y	Y
Arya et al., 2016	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Ashmawi et al., 2016	Low	Y	Y	Low	High	Y	N	N	High	Low	Y	PY	Y	Y
Beydoun et al., 2015	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Blank et al., 2021	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Y
Bruun et al., 2016	Low	Y	Y	Low	Low	Y	N	N	High	Low	Y	Y	Y	Y
Cerulli Irelli et al., 2022	Low	Y	PY	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Chen et al., 2017	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Y
Chen et al., 2021	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Dlugos and Buono, 2004	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Dlugos et al., 2013	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PN	Y	Y
Dragoumi et al., 2013	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PN	Y	NI
Gasparini et al., 2013	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Gidey et al., 2020	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Hersi et al., 2021	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Hitiris et al., 2007	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Huang et al., 2016	Low	Y	Y	Low	Low	Y	N	Y	High	High	Y	PN	Y	Y
Jiang et al., 2017	Low	Y	Y	Low	High	Y	N	N	High	Low	Y	PN	Y	Y
Kessler et al., 2017	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	PN	Y	Y
Kim et al., 2017	Low	PN	Y	High	Low	Y	N	Y	High	Low	Y	PY	Y	Y
Kwong et al., 2007	Low	Y	Y	Low	High	Y	N	N	High	Low	Y	PY	Y	Y
Li et al., 2021	Low	Y	Y	Low	High	Y	N	N	High	Low	Y	PN	Y	Y
Mangunatmadja et al., 2021	Low	Y	Y	Low	High	Y	N	N	High	High	Y	PN	Y	Y
Ollivier et al., 2009	Low	Y	Y	Low	High	Y	N	N	High	Low	Y	PY	Y	Y
Oskoui et al., 2005	Low	Y	Y	Low	High	Y	N	N	High	Low	Y	PN	N	Y
Park et al., 2014	Low	Y	Y	Low	Low	Y	N	Y	High	Low	PY	PN	Y	Y
Quintana et al., 2021	Low	Y	Y	Low	Low	PN	N	Y	High	Low	Y	Y	Y	Y
Sharma et al., 2021	Low	Y	Y	Low	Low	PN	N	Y	High	Low	Y	PY	Y	Y
Sillanpää and Shinnar, 2002	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Y
Tartara et al., 2022	Low	Y	Y	Low	Low	PN	N	Y	High	Low	Y	NI	Y	Y
Yang et al., 2020	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Y
Zhang et al., 2013	Low	Y	Y	Low	High	Y	N	N	High	Low	Y	PY	Y	Y

Note: Responses, in order of low to high risk of bias: Y, yes; PY, probably yes; NI, no information; PN, probably no; N, no. x.a. indicates domain applicability; x.b., indicates domain risk of bias.[10,26,29,47–75]

stratification. For example, all six of the generalized epilepsy studies in our sample were included in the childhood epilepsy strata, and our sample was not large enough to allow for syndrome-specific interpretations. With a large enough sample, strata would ideally conform to the diagnostic labels specified by the ILAE, necessitating a systematic approach and greater stringency when describing and selecting for recruitment.[40]

4.1.3 | Bias and applicability concerns

The models in our sample were found to contain universally high RoB. Initially, it seems unlikely that models created in a clinical context could be entirely free of RoB. For example, signaling questions 2.2 and 3.5 in the PROBAST tool relate to the blinding of outcomes and predictors, respectively, which were systematic

3.5	3.6	3.b	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	4.b	Total.a	Total.b
N	Y	High	N	Y	Y	NI	N	NI	N	NI	NI	High	Low	High
PY	PN	High	Y	Y	N	PN	NI	NI	NI	NI	NI	High	Low	High
N	Y	High	N	N	PY	PN	N	NI	N	NI	NI	High	High	High
N	Y	High	PN	N	PY	NI	NI	NI	NI	NI	NI	High	Low	High
N	Y	High	Y	N	N	PN	Y	PN	NI	NI	NI	High	Low	High
N	Y	High	PN	N	N	NI	Y	PN	NI	NI	NI	High	Low	High
N	PY	High	N	Y	N	PN	N	NI	NI	NI	NI	High	Low	High
N	Y	High	Y	Y	Y	PN	N	NI	NI	NI	NI	High	Low	High
N	Y	High	N	N	Y	PN	N	NI	NI	NI	NI	High	Low	High
N	Y	High	N	N	PY	PN	N	NI	NI	NI	NI	High	Low	High
N	PY	High	PN	N	N	PN	NI	NI	N	PN	NI	High	Low	High
N	Y	High	N	N	Y	PN	N	NI	N	NI	NI	High	Low	High
N	Y	High	N	N	Y	PN	N	NI	NI	NI	NI	High	Low	High
N	Y	High	PY	N	Y	PN	N	NI	NI	NI	NI	High	Low	High
N	Y	High	Y	Y	PY	PN	Y	NI	NI	NI	NI	High	Low	High
N	Y	High	Y	N	Y	PN	Y	NI	NI	NI	NI	High	Low	High
N	Y	High	N	N	N	PN	NI	NI	NI	NI	NI	High	High	High
N	Y	High	N	N	Y	PN	N	NI	NI	NI	NI	High	High	High
N	PY	High	NI	NI	N	N	NI	NI	N	NI	NI	High	Low	High
N	Y	High	N	Y	Y	PN	Y	NI	NI	NI	NI	High	Low	High
N	PY	High	N	Y	PN	PN	N	NI	NI	NI	NI	High	High	High
N	Y	High	N	N	Y	PN	N	NI	NI	NI	NI	High	High	High
N	Y	High	N	N	Y	PN	N	NI	NI	NI	NI	High	High	High
N	NI	High	N	N	PY	PN	N	NI	NI	NI	NI	High	High	High
N	PN	High	N	N	PN	PN	Y	NI	NI	NI	NI	High	High	High
N	PN	High	N	N	Y	PN	Y	NI	NI	NI	NI	High	Low	High
N	Y	High	N	Y	Y	PN	N	NI	NI	NI	NI	High	Low	High
N	Y	High	PY	N	PN	N	N	NI	NI	NI	NI	High	Low	High
N	PY	High	N	N	PN	N	Y	NI	NI	NI	NI	High	Low	High
N	Y	High	N	Y	Y	PN	NI	NI	NI	NI	NI	High	Low	High
N	PN	High	PY	Y	PY	Y	N	NI	N	PN	NI	High	Low	High
N	Y	High	N	N	PN	N	N	NI	NI	NI	NI	High	High	High

vulnerabilities for RoB in our sample and are particularly difficult to avoid in retrospective and cross-sectional studies.[36] With appropriate reporting of data collection time points and outcome definitions, however, it may in some cases be inferred that data were collected "blinded to the outcome" or for "objective outcomes," which would allow for a low RoB rating regardless of actual "blinding." Outcome objectivity is also related to signaling question 3.2 ("Was a prespecified or standard outcome definition used?"), which had mixed ratings in our assessment. More consistent adoption of the ILAE definition of drug responsiveness/treatment outcome ("seizure-free for a minimum of three times the longest pretreatment interseizure interval, or 12 months, whichever is longer") would offset the subjectivity introduced by some of the outcome definitions in our

sample, and therefore reduce RoB levels.[11] Furthermore, inferred objectivity could be reinforced by avoiding convenience-based decisions when designing studies, that is, using a homogenous, predetermined time point, instead of the last available follow-up. In our sample, information required to evaluate domain 4 ("Analysis") of the PROBAST assessment was often not reported.[36] Adherence to the modeling guidelines of TRIPOD by journal editors (similar to CONSORT [Consolidated Standards of Reporting Trials]) and researchers, and nominal acknowledgment of best practices, such as clearly reporting model characteristics, would facilitate research communication and uptake.[76]

A subset of the included studies also exhibited applicability concerns, indicative of a lack of consistency between study objectives and methods. An adverse effect of low applicability is heterogeneity of study characteristics. Although a study without applicability concerns can still introduce variance into a review, data high in applicability is complementary, addressing preexisting variability. In consideration of the vast number of potential measurements of treatment outcomes in the literature, our inclusion criteria were intentionally lenient, at the cost of outcome heterogeneity precluding quantitative synthesis of our findings. For example, although 2 months of posttreatment seizure freedom may not classify for remission, for PWE who previously experienced multiple seizures per day, 2 months of freedom is a noteworthy outcome that may not have been appropriately captured. Alongside offering a standardized (objective) outcome measurement, the previously mentioned ILAE definition for treatment outcome would help to contextualize the posttreatment profile of a PWE with their pretreatment factors, and encourage applicability.[11] The development of a Core Outcome Set for NDE, and the use of predefined predictors, outcomes, and time points will help to minimize applicability concerns in future studies.[77,78]

4.2 | Limitations

Whereas all individuals with new onset epilepsy have (by definition) NDE, the inverse is not true; some PWE may have an undisclosed or unreported history of seizures, extending beyond the recommended 12-month cutoff.[14] In consideration of its distinction from NDE, this review has purposefully avoided misattributing any samples as "new-onset epilepsy," instead opting for the more verifiable NDE label. With this omission comes a potential loss of specificity that may hamper the accuracy of the presented model to certain PWE; guidelines for reporting seizure histories have been suggested, which should help to prevent this necessity in future reports.[79]

By including only studies involving a discrete sample of ILAE-compliant NDE, this review addresses a sample who are not vulnerable to the common confounds of epilepsy research (such as ASM use and chronicity) or the heterogeneity of broader seizure research.[14] However, this specificity comes at the cost of generalizability to provoked seizure research. The exploration of febrile, traumatic, and other acute seizure activity also has the potential to elucidate the pathomechanisms of ictogenesis, with ostensible benefit to unprovoked seizure research. The two categories of predictors that were the strongest prognostic factors of epileptic seizure remission in this review, history and seizure characteristics, allude to pathomechanistic vulnerabilities (respectively, a predisposition to ictogenesis and the seizure insult) that could potentially describe provocation once fully understood. The conclusions of this review should be weighed against those of reviews on early and first seizures of mixed etiology to fully understand the influence of precipitation on ictogenesis.[41,80]

ML is a rapidly expanding field in the health data sciences that has demonstrated widespread potential utility.[42] Our decision not to include ML studies in this review was based on several factors. Although reporting guidelines (TRIPOD-AI and PROBAST-AI) are in development, current reporting standards in ML prediction model studies are lacking.[43] Due in part to their novelty, many ML studies are still "proof of concept," and rely on sensitive data that preclude transparency. Beyond issues with the generalizability of models that rely on training data, the same methodological critiques leveled toward conventional prediction modeling studies can also apply to ML studies, suggesting that our current methods of evaluating RoB and accessibility concerns are insufficient to handle them. Alongside bias assessment, this review presents a narrative synthesis of factors commonly reported as significantly associated with treatment outcomes in NDE. The "black box" nature of ML currently precludes this level of granularity. Consequently, our search strategy was not optimized to capture ML prediction models. However, as we did not explicitly exclude ML studies at the search phase, we have summarized the few that would have otherwise passed screening in Appendix E. That ML studies were omitted from the bulk of this review should not be taken as a dismissal of their increasing value to prognosis and diagnosis, but rather as a necessary step to ensure the comparability of the included regression model studies. Further exploration beyond the scope of this study is necessary to evaluate the current state of ML prediction modeling in epilepsy and guide future studies.

Electrophysiology and MRI are often collected as part of the clinical pathway for epilepsy. However, this has not appeared to have resulted in an overrepresentation of

EEG- or MRI-related predictive factors. There are several potential reasons for this, such as the relative difficulty/cost of quantifying EEG and MRI findings, or the variability within these methods. Regardless, despite the growing popularity of imaging methods for the study of epilepsy, and the large amount of data offered by imaging, the included studies report few significant associations related to either category. Imaging data may be underrepresented in this sample.

5 | CONCLUSIONS

The studies included in this review are heterogenous in both predictor and outcome selection, which is a hindrance to systematic comparison. To evaluate their effectiveness, a guideline-based approach to prediction modeling of treatment outcomes should be encouraged, whereas the inclusion of response to treatment as a prognostic factor at baseline should be avoided. Authors should also attempt to ensure that they report all study characteristics and modeling parameters, to reduce RoB and applicability concerns.

AUTHOR CONTRIBUTIONS

Corey Ratcliffe: Conceptualization; investigation; visualization; writing–original draft preparation; writing–review and editing. **Vishnav Pradeep:** Investigation. **Anthony Marson:** Writing–review and editing. **Simon S. Keller:** Writing–review and editing; supervision. **Laura J. Bonnett:** Conceptualization; investigation; writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

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

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APPENDIX A

A.1 | Appendix

MEDLINE search strategy (Medical Subject Headings), carried out on August 24, 2022.

1. early diagnosis/
2. ((recent$ or new$ or early) adj2 (diagnos$ or onset)).tw.
3. ("first seizure" or "first fit").tw.
4. 1 or 2 or 3
5. exp Epilepsy/ or epilep$.tw.
6. (validation studies or clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv or comparative study or evaluation studies or multicenter study).pt.
7. ((observation$ or cohort or case$ or cross? section$ or "cross section$" or "time-series" or "time series" or "before and after" or "before-and-after" or retrospective) adj2 (study or trial or method)).mp.
8. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.
9. clinical trials as topic.sh.
10. trial.ti.
11. 6 or 7 or 8 or 9 or 10
12. exp animals/ not humans.sh.
13. 11 not 12
14. 13 not case reports.pt.
15. Validat$.mp. or Predict$.ti. or Rule$.mp. or (Predict$ and (Outcome$ or Risk$ or Model$)).mp. or ((History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$) and (Predict$ or Model$ or Decision$ or Indentif$ or Prognos$)).mp. or (Decision$.mp. and ((Model$ or Clinical$).mp. or Logistic Models/)) or (Prognostic and (History or Variable$ or Criteria or Scor$ or

```
Characteristic$ or Finding$ or Factor$ or
Model$)).mp. [mp=title, book title, ab-
stract, original title, name of substance
word, subject heading word, floating sub-
heading word, keyword heading word, organ-
ism supplementary concept word, protocol
supplementary concept word, rare disease
supplementary concept word, unique iden-
tifier, synonyms]
16. 5 and 14 and 15
17. 4 and 16
```

A.2 | Appendix

SCOPUS search strategy (Boolean), carried out on November 14, 22.

```
(
    (
        TITLE-ABS-KEY("early diagnosis")
        OR
       TITLE-ABS-KEY((recent* OR new* OR
early*) Pre/0 (diagnos* OR onset))
        OR
        TITLE-ABS-KEY("first seizure" OR
"first fit")
    )
                                        AND
    DOCTYPE(AR)
    AND
    (
        TITLE-ABS-KEY(Epilep*)
        AND
        (
            (
              TITLE-ABS-KEY((observation
OR cohort OR case OR "cross section*" OR
"time series" OR "before and after" OR
retrospective) Pre/0 (study OR trial OR
method))
                OR
               ABS("randomized controlled
trial" OR "controlled clinical trial" OR
randomized OR placebo OR randomly)
                OR
                KEY("clinical trial")
                OR
                TITLE(trial)
                )
            AND NOT
            ALL(animal OR "case report")
        )
        AND
        (
          TITLE-ABS-KEY(validat* OR rule*
OR (Predict* AND (Outcome* OR Risk* OR
Model*)) OR ((History OR Variable$ OR
Criteria OR Scor* OR Characteristic*
OR Finding* OR Factor*) AND (Predict*
OR Model* OR Decision* OR Indentif* OR
Prognos*)) OR (Decision* AND ((Model*
OR Clinical*) OR "Logistic Models")) OR
(Prognostic AND (History OR Variable* OR
Criteria OR Scor* OR Characteristic* OR
Finding* OR Factor* OR Model*)))
          OR
          TITLE(predict*)
          )
    )
)
```

APPENDIX B

Predictors

- Age: Factors derived from the age of the patient at diagnosis or seizure onset. Not the same as disease duration.
- Antiseizure medication (ASM): Factors derived from treatment with ASM, such as first-line therapy or ASM change.
- Comorbidity: Factors derived from the presence of a concurrent medical, neuropsychological, or neuropsychiatric condition. Likely operationalized as an ordinal or nominal variable.
- Demographics: Factors derived from the patient's nonclinical psychosocial environment, excluding age.
- Diagnosis: Factors derived from the patient's clinical diagnosis with an epilepsy disorder. Likely inferential, based on age, semiology, electroencephalography (EEG), neuroimaging, and history.
- EEG: Factors derived from functional brain activity data generated with EEG or magnetoencephalography.
- History: Factors derived from the clinical history of the patient and the patient's family.
- Neuroimaging: Factors derived from any of the following imaging paradigms, in isolation or combination: magnetic resonance imaging, positron emission tomography, computerized tomography.
- Neuropsychology: Factors derived from subclinical neuropsychological performance. Likely operationalized on a continuous scale of performance.
- Response: Factors derived from the patient's response (disease course) following a medical intervention/treatment plan, i.e., a prescription of ASM.
- Seizure characteristics/types: Factors relating to the dynamics and properties of the seizures experienced by the patient. Not always the same as diagnosis.

Outcomes

- Mortality: Endpoints referring to patient death/rate of death, either disease-related or otherwise, at any time point.
- Drug resistance: Endpoints referring to intractability, refractoriness, or poor outcomes in the long term (≥12 months).
- Seizure remission: Endpoints referring to seizure freedom or remission in the long term (≥12 months).
- Short-term treatment response: Endpoints referring to short term (<12 months) response (disease course) following a medical intervention/treatment plan, i.e., a prescription of ASM.

APPENDIX C

Detailed study demographics.

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Aikiä et al., 1999	Refractory seizure disorder	Drug resistance	Positive	Reduced chance of drug resistance	NA	No significant predictors	NA
Aikiä et al., 1999	Refractory seizure disorder	Drug resistance	Negative	Increased chance of drug resistance	Age at diagnosis (younger = greater likelihood of poor 2-year outcome)	Younger at diagnosis	Age
Aikiä et al., 1999	Refractory seizure disorder	Drug resistance	Negative	Increased chance of drug resistance	Etiology (remote symptomatic = greater likelihood of poor 2-year outcome)	Remote symptomatic etiology	Diagnosis
Aikiä et al., 1999	Refractory seizure disorder	Drug resistance	Negative	Increased chance of drug resistance	Seizure type (partial complex or mixed = greater likelihood of poor 2-year outcome)	Partial complex or mixed seizures	Seizure characteristics/types
Aikiä et al., 1999	Refractory seizure disorder	Drug resistance	Negative	Increased chance of drug resistance	Spike focus (presence = greater likelihood of poor 2-year outcome)	Spike focus	EEG
Aikiä et al., 1999	Refractory seizure disorder	Drug resistance	Negative	Increased chance of drug resistance	Immediate list recall (impairment = greater likelihood of poor 2-year outcome)	Impaired short-term memory	Comorbidity
Aikiä et al., 1999	Refractory seizure disorder	Drug resistance	Negative	Increased chance of drug resistance	Delayed list recognition (impairment = greater likelihood of poor 2-year outcome)	Impaired long-term memory	Comorbidity
Arya et al., 2016	Freedom from failure	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Arya et al., 2016	Freedom from failure	Short-term treatment response	Negative	Impaired short-term treatment response	ASM (LTG = reduced chance of freedom from failure)	Treated with LTG	ASM
Arya et al., 2016	Seizure freedom	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Arya et al., 2016	Seizure freedom	Short-term treatment response	Negative	Impaired short-term treatment response	ASM (LTG = reduced chance of seizure freedom)	Treated with LTG	ASM
Ashmawi et al., 2016	2-year seizure remission	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Ashmawi et al., 2016	2-year seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	Nocturnal seizures (yes = reduced chance of sustained 2-year remission)	Nocturnal seizures	Seizure characteristics/ types
Ashmawi et al., 2016	2-year seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	First ASM response (bad = reduced chance of 2-year remission)	Poor ASM response	Response
Ashmawi et al., 2016	2-year sustained seizure remission	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Ashmawi et al., 2016	2-year sustained seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	First ASM response (bad = reduced chance of 2-year sustained remission)	Poor ASM response	Response
Beydoun et al., 2015	6-month terminal seizure remission at month 12	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Beydoun et al., 2015	6-month terminal seizure remission at month 12	Seizure remission	Negative	Reduced chance of seizure remission	Epileptogenic lesion on neuroimaging (yes = less likely to experience 6-month terminal remission at month 12)	Presence of epileptogenic lesion	Neuroimaging
Beydoun et al., 2015	6-month terminal seizure remission at month 12	Seizure remission	Negative	Reduced chance of seizure remission	Baseline seizure type (simple partial = less likely to experience 6-month terminal remission at month 12)	Simple partial seizures	Seizure characteristics/ types
Blank et al., 2021	5-year mortality	Mortality	Positive	Reduced chance of mortality	Sex (female = decreased risk of mortality)	Female sex	Demographics
Blank et al., 2021	5-year mortality	Mortality	Positive	Reduced chance of mortality	Race (Asian = decreased risk of mortality)	Asian race	Demographics
Blank et al., 2021	5-year mortality	Mortality	Positive	Reduced chance of mortality	Ethnicity (Hispanic = decreased risk of mortality)	Hispanic ethnicity	Demographics
Blank et al., 2021	5-year mortality	Mortality	Negative	Increased chance of mortality	Comorbidity (yes = increased risk of mortality)	Presence of comorbidity	Comorbidity
Blank et al., 2021	5-year mortality	Mortality	Negative	Increased chance of mortality	Medicaid coinsurance (yes = increased risk of mortality)	Applicable for Medicaid	Demographics
Blank et al., 2021	5-year mortality	Mortality	Negative	Increased chance of mortality	Rural–urban continuum code (intermediate = increased risk of mortality)	Intermediate urbanization of residence	Demographics
Bruun et al., 2016	2-year seizure remission	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Bruun et al., 2016	2-year seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	Seizure remission within the first year of ASM treatment (no = less likely to attain 2-year remission)	Poor ASM response	Response

(Continues)

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Bruun et al., 2016	5-year seizure remission	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Bruun et al., 2016	5-year seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	NA	No significant predictors	NA
Cerulli Irelli et al., 2022	4-year seizure remission	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Cerulli Irelli et al., 2022	4-year seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	Absence seizures (present = lower remission probability)	Absence seizures	Seizure characteristics/ types
Cerulli Irelli et al., 2022	Delayed seizure remission	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Cerulli Irelli et al., 2022	Delayed seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	Age at onset (earlier = remission delay)	Younger at diagnosis	Age
Cerulli Irelli et al., 2022	Delayed seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	Catamenial seizures (present = remission delay)	Catamenial seizures	Seizure characteristics/ types
Chen et al., 2017	Terminal seizure outcome	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Chen et al., 2017	Terminal seizure outcome	Seizure remission	Negative	Reduced chance of seizure remission	Seizures in the year prior to treatment (more = poorer chance of seizure freedom)	Pretreatment seizures	Seizure characteristics/ types
Chen et al., 2017	Terminal seizure outcome	Seizure remission	Negative	Reduced chance of seizure remission	Recreational drug use (yes = poorer chance of seizure freedom)	Recreational drug use	Comorbidity
Chen et al., 2017	Terminal seizure outcome	Seizure remission	Negative	Reduced chance of seizure remission	Family history of epilepsy (more = poorer chance of seizure freedom)	Family history of epilepsy	History
Chen et al., 2021	Treatment response	Short-term treatment response	Negative	Impaired short-term treatment response	Age at onset (<5 years = lower likelihood of treatment response)	Unknown etiology	Age
Chen et al., 2021	Treatment response	Short-term treatment response	Negative	Impaired short-term treatment response	Attack frequency (higher = lower likelihood of treatment response)	Higher pretreatment seizure frequency	Seizure characteristics/ types
Chen et al., 2021	Treatment response	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Dlugos and Buono, 2004	Persistence of LOC seizures at a maximally tolerated dose of CBZ within 1 year of initiation	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Dlugos and Buono, 2004	Persistence of LOC seizures at a maximally tolerated dose of CBZ within 1 year of initiation	Short-term treatment response	Negative	Impaired short-term treatment response	Early risk factor for epilepsy (yes = higher chance of trial failure)	Presence of epilepsy risk factor	Neuroimaging
Dlugos and Buono, 2004	Persistence of LOC seizures at a maximally tolerated dose of CBZ within 1 year of initiation	Short-term treatment response	Negative	Impaired short-term treatment response	Temporal neuroimaging abnormality (yes = higher chance of trial failure)	Presence of temporal epileptogenic lesion	Neuroimaging
Dlugos et al., 2013	Freedom from failure at 16–20 weeks	Short-term treatment response	Positive	Improved short-term treatment response	ASM (ETX over LTG = greater chance of freedom from failure)	Treated with ETX	ASM
Dlugos et al., 2013	Freedom from failure at 16–20 weeks	Short-term treatment response	Positive	Improved short-term treatment response	Shortest seizure duration (Longer = greater chance of freedom from failure)	Longer minimum seizure duration	Seizure characteristics/ types
Dlugos et al., 2013	Freedom from failure at 16–20 weeks	Short-term treatment response	Negative	Impaired short-term treatment response	NA	No significant predictors	NA
Dlugos et al., 2013	Seizure freedom at 16–20 weeks	Short-term Treatment Response	Positive	Improved short-term treatment response	ASM (ETX over LTG = greater chance of seizure freedom)	Treated with ETX	ASM
Dlugos et al., 2013	Seizure freedom at 16–20 weeks	Short-term treatment response	Positive	Improved short-term treatment response	Shortest seizure duration (longer = greater chance of seizure freedom)	Longer minimum seizure duration	Seizure characteristics/ types
Dlugos et al., 2013	Seizure freedom at 16–20 weeks	Short-term treatment response	Negative	Impaired short-term treatment response	NA	No significant predictors	NA
Dragoumi et al., 2013	12-month seizure remission at 2 years	Seizure remission	Positive	Increased chance of seizure remission	Diagnosis (CAE = increased chance of remission at 2 years)	Diagnosis of CAE	Diagnosis
Dragoumi et al., 2013	12-month seizure remission at 2 years	Seizure remission	Positive	Increased chance of seizure remission	Response (early = increased chance of remission at 2 years)	Early response	Response
Dragoumi et al., 2013	12-month seizure remission at 2 years	Seizure remission	Negative	Reduced chance of seizure remission	NA	No significant predictors	NA
Dragoumi et al., 2013	Occurrence of seizures in the initial 12 months	Short-term treatment response	Positive	Improved short-term treatment response	Age at onset (older = decreased chance of seizure occurrence in the first 12 months)	Older at diagnosis	Age
Dragoumi et al., 2013	Occurrence of seizures in the initial 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Status epilepticus (yes = increased chance of seizure occurrence in the first 12 months)	Status epilepticus	Seizure characteristics/ types

(Continues)

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Dragoumi et al., 2013	Occurrence of seizures in the initial 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Multiple seizure types (more = increased chance of seizure occurrence in the first 12 months)	Multiple pretreatment seizure types	Seizure characteristics/types
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at 4 years	Seizure remission	Positive	Increased chance of seizure remission	Academic performance (high = decreased chance of seizure occurrence in the preceding 2 years at 4 years)	High academic performance	Neuropsychology
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at 4 years	Seizure remission	Negative	Reduced chance of seizure remission	History of febrile seizures (yes = increased chance of seizure occurrence in the preceding 2 years at 4 years)	History of febrile seizures	History
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at 4 years	Seizure remission	Negative	Reduced chance of seizure remission	History of migraine (yes = increased chance of seizure occurrence in the preceding 2 years at 4 years)	History of migraine	History
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at study end	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at study end	Seizure remission	Negative	Reduced chance of seizure remission	Multiple seizure types (more = increased chance of seizure occurrence in the preceding 2 years at study end)	Multiple pretreatment seizure types	Seizure characteristics/types
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at study end	Seizure remission	Negative	Reduced chance of seizure remission	Early response (no = increased chance of seizure occurrence in the preceding 2 years at study end)	Poor ASM response	Response
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at study end	Seizure remission	Negative	Reduced chance of seizure remission	History of migraine (yes = increased chance of seizure occurrence in the preceding 2 years at study end)	History of migraine	History
Dragoumi et al., 2013	Occurrence of seizures in the preceding 2 years at study end	Seizure remission	Negative	Reduced chance of seizure remission	Initial response to treatment (no = increased chance of seizure occurrence in the preceding 2 years at study end)	Poor ASM response	Response
Dragoumi et al., 2013	Remission–relapse pattern	Seizure remission	Positive	Increased chance of seizure remission	Age at onset (older = decreased chance pattern C)	Older at diagnosis	Age
Dragoumi et al., 2013	Remission–relapse pattern	Seizure remission	Positive	Increased chance of seizure remission	Response (early = decreased chance pattern C)	Early response	Response

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Dragoumi et al., 2013	Remission–relapse pattern	Seizure remission	Positive	Increased chance of seizure remission	Response (immediate = decreased chance pattern C)	Early response	Response
Dragoumi et al., 2013	Remission–relapse pattern	Seizure remission	Negative	Reduced chance of seizure remission	Multiple seizure types (more = increased chance of pattern C)	Multiple pretreatment seizure types	Seizure characteristics/ types
Dragoumi et al., 2013	Remission–relapse pattern	Seizure remission	Negative	Reduced chance of seizure remission	History of migraine (yes = increased chance of pattern C)	History of migraine	History
Gasparini et al., 2013	5-year seizure remission	Seizure remission	Positive	Increased chance of seizure remission	Family history (epilepsy or febrile seizures = increased chance of remission)	Family history of seizures	History
Gasparini et al., 2013	5-year seizure remission	Seizure remission	Positive	Increased chance of seizure remission	Lobe localization (front = increased chance of remission)	Frontal focus	Seizure characteristics/ types
Gasparini et al., 2013	5-year seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	NA	No significant predictors	NA
Gidey et al., 2020	Seizure recurrence	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Gidey et al., 2020	Seizure recurrence	Short-term treatment response	Negative	Impaired short-term treatment response	Pretreatment seizure number (greater = decreased chance of achieving seizure remission)	Higher pretreatment seizure count	Seizure characteristics/ types
Gidey et al., 2020	Seizure recurrence	Short-term treatment response	Negative	Impaired short-term treatment response	Treatment adherence (poor = decreased chance of achieving seizure remission)	Low treatment adherence	Response
Hersi et al., 2021	12-month seizure remission	Seizure remission	Positive	Increased chance of seizure remission	Sex (male = more likely to achieve remission)	Male sex	Demographics
Hersi et al., 2021	12-month seizure remission	Seizure remission	Positive	Increased chance of seizure remission	Etiology (unknown = more likely to achieve remission)	Unknown etiology	Diagnosis
Hersi et al., 2021	12-month seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	EEG (epileptiform activity = less likely to achieve seizure freedom)	Presence of epileptiform activity	EEG
Hitiris et al., 2007	Seizure-free for the past 12 months	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Hitiris et al., 2007	Seizure-free for the past 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Family history–epilepsy (Yes = greater risk of drug resistance)	Family history of epilepsy	History
Hitiris et al., 2007	Seizure-free for the past 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	History of febrile seizures (yes = greater risk of drug resistance)	History of febrile seizures	History
Hitiris et al., 2007	Seizure-free for the past 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Traumatic brain injury (yes = greater risk of drug resistance)	Presence of traumatic brain injury	Neuroimaging

(Continues)

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Hitiris et al., 2007	Seizure-free for the past 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Psychiatric comorbidity (yes = greater risk of drug resistance)	Presence of psychiatric comorbidity	Comorbidity
Hitiris et al., 2007	Seizure-free for the past 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Recreational drug use (yes = greater risk of drug resistance)	Recreational drug use	Comorbidity
Hitiris et al., 2007	Seizure-free for the past 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	More than 10 seizures before treatment (yes = greater risk of drug resistance)	Higher pretreatment seizure count	Seizure characteristics/ types
Huang et al., 2016	50% seizure reduction	Short-term treatment response	Positive	Improved short-term treatment response	Age at onset (older = more likely to achieve satisfactory seizure control at 2 years)	Older at diagnosis	Age
Huang et al., 2016	50% seizure reduction	Short-term treatment response	Positive	Improved short-term treatment response	ASM treatment (yes = more likely to achieve satisfactory seizure control at 2 years)	Treated with ASM	ASM
Huang et al., 2016	50% seizure reduction	Short-term treatment response	Negative	Impaired short-term treatment response	NA	No significant predictors	NA
Jiang et al., 2017	2-year seizure remission at short-term follow-up	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Jiang et al., 2017	2-year seizure remission at short-term follow-up	Seizure remission	Negative	Reduced chance of seizure remission	Time to treatment (>12 months = more likely to experience unfavorable short-term outcomes)	Delayed treatment onset	Response
Jiang et al., 2017	2-year seizure remission at short-term follow-up	Seizure remission	Negative	Reduced chance of seizure remission	Seizure frequency in the first year of treatment (>2 = more likely to experience unfavorable short-term outcomes)	Poor ASM response	Response
Jiang et al., 2017	5-year seizure remission at long-term follow-up	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Jiang et al., 2017	5-year seizure remission at long-term follow-up	Seizure remission	Negative	Reduced chance of seizure remission	Seizure frequency in the first year of treatment (>2 = more likely to experience unfavorable long-term outcomes)	Poor ASM response	Response
Kessler et al., 2017	Seizure freedom at 16–20 weeks	Short-term treatment response	Positive	Improved short-term treatment response	Shortest burst duration on baseline EEG (short = higher chance of seizure freedom)	Shorter EEG bursts	EEG
Kessler et al., 2017	Seizure freedom at 16–20 weeks	Short-term treatment response	Negative	Impaired short-term treatment response	LTG vs ETX (LTG = lower chance of seizure freedom)	Treated with LTG	ASM
Kessler et al., 2017	Seizure freedom at 16–20 weeks	Short-term treatment response	Negative	Impaired short-term treatment response	Cluster pattern 2 (yes = lower chance of seizure freedom)	Noneye automatisms	Seizure characteristics/ types

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Kessler et al., 2017	Seizure freedom at 16–20 weeks	Short-term treatment response	Negative	Impaired short-term treatment response	Cluster pattern 2/4 (yes = lower chance of seizure freedom)	Noneye automatisms or myoclonic/atonic/clonic seizures	Seizure characteristics/types
Kim et al., 2017	<6 months of continuous seizure freedom	Short-term treatment response	Positive	Improved short-term treatment response	Corpus callosum volume (lower = good ASM response)	Lower corpus callosum volumes	Neuroimaging
Kim et al., 2017	<6 months of continuous seizure freedom	Short-term treatment response	Negative	Impaired short-term treatment response	NA	No significant predictors	NA
Kwong et al., 2007	Seizure freedom	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Kwong et al., 2007	Seizure freedom	Short-term treatment response	Negative	Impaired short-term treatment response	Acute seizure-related hospitalizations (yes = more likely not to achieve seizure freedom)	Acute seizure-related hospitalizations	Seizure characteristics/types
Li et al., 2021	3-year seizure freedom	Drug resistance	Positive	Reduced chance of drug resistance	NA	No significant predictors	NA
Li et al., 2021	3-year seizure freedom	Drug resistance	Negative	Increased chance of drug resistance	Seizure types (multiple = greater chance of poor drug response)	Multiple pretreatment seizure types	Seizure characteristics/types
Li et al., 2021	3-year seizure freedom	Drug resistance	Negative	Increased chance of drug resistance	Polytherapy (yes = greater chance of poor drug response)	Treated with polytherapy	ASM
Mangunatmadja et al., 2021	Intractable epilepsy	Drug resistance	Positive	Reduced chance of drug resistance	NA	No significant predictors	NA
Mangunatmadja et al., 2021	Intractable epilepsy	Drug resistance	Negative	Increased chance of drug resistance	Seizure-type evolution (generalization at study end = greater chance of intractability)	Evolution to generalized seizures	Seizure characteristics/types
Mangunatmadja et al., 2021	Intractable epilepsy	Drug resistance	Negative	Increased chance of drug resistance	Background rhythm evolution (abnormal at study end = greater chance of intractability)	Evolution to abnormal background rhythm	EEG
Ollivier et al., 2009	Complete disappearance of absence seizures during VPA treatment	Short-term treatment response	Positive	Improved short-term treatment response	Age at diagnosis (older = protective factor against nonresponsiveness to VPA)	Older at diagnosis	Age
Ollivier et al., 2009	Complete disappearance of absence seizures during VPA treatment	Short-term treatment response	Negative	Impaired short-term treatment response	Pretreatment seizure frequency > 10/day (yes = risk factor for nonresponsiveness to VPA)	Higher pretreatment seizure frequency	Seizure characteristics/types
Ollivier et al., 2009	Complete disappearance of absence seizures during VPA treatment	Short-term treatment response	Negative	Impaired short-term treatment response	Presence of GTCS (yes = risk factor for nonresponsiveness to VPA)	Presence of GTCS	Seizure characteristics/types

(Continues)

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Ollivier et al., 2009	Long-term seizure freedom	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Ollivier et al., 2009	Long-term seizure freedom	Seizure remission	Negative	Reduced chance of seizure remission	NA	No significant predictors	NA
Oskoui et al., 2005	Lower probability of seizure remission at 12 months	Drug resistance	Positive	Reduced chance of drug resistance	NA	No significant predictors	NA
Oskoui et al., 2005	Lower probability of seizure remission at 12 months	Drug resistance	Negative	Increased chance of drug resistance	More than one seizure type (yes = increased chance of intractability at 12 months)	Multiple pretreatment seizure types	Seizure characteristics/ types
Oskoui et al., 2005	Lower probability of seizure remission at 12 months	Drug resistance	Negative	Increased chance of drug resistance	Seizure recurrence in the 6–12 months posttreatment (yes = increased chance of intractability at 12 months)	Poor ASM response	Response
Oskoui et al., 2005	Lower probability of seizure remission at 12 months	Drug resistance	Negative	Increased chance of drug resistance	Mental retardation (yes = increased chance of intractability at 12 months)	Presence of intellectual disability	Comorbidity
Oskoui et al., 2005	Lower probability of seizure remission at 3 months	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Oskoui et al., 2005	Lower probability of seizure remission at 3 months	Short-term treatment response	Negative	Impaired short-term treatment response	More than one seizure type (yes = increased chance of intractability at 3 months)	Multiple pretreatment seizure types	Seizure characteristics/ types
Oskoui et al., 2005	Poor outcome at 12 months	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Oskoui et al., 2005	Poor outcome at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	More than one seizure type (yes = increased chance of poor outcome at 12 months)	Multiple pretreatment seizure types	Seizure characteristics/ types
Oskoui et al., 2005	Poor outcome at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Global developmental delay at onset (yes = increased chance of poor outcome at 12 months)	Presence of global developmental delay	Comorbidity
Oskoui et al., 2005	Poor outcome at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Seizure recurrence in the 6–12 months posttreatment (yes = increased chance of poor outcome at 12 months)	Poor ASM response	Response
Oskoui et al., 2005	Poor outcome at 3 months	Short-term treatment response	Positive	Improved short-term treatment response	Diagnosis (IGE = decreased chance of poor outcome at 3 months)	Diagnosis of IGE	Diagnosis
Oskoui et al., 2005	Poor outcome at 3 months	Short-term treatment response	Negative	Impaired short-term treatment response	More than one seizure type (yes = increased chance of poor outcome)	Multiple pretreatment seizure types	Seizure characteristics/ types

APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Oskoui et al., 2005	Poor outcome at 3 months	Short-term treatment response	Negative	Impaired short-term treatment response	Global developmental delay at onset (yes = increased chance of poor outcome at 3 months)	Presence of global developmental delay	Comorbidity
Park et al., 2014	Seizure-free for the past 6 months	Short-term treatment response	Positive	Improved short-term treatment response	Age at onset (16+ years = increased chance of being a responder)	Older at diagnosis	Age
Park et al., 2014	Seizure-free for the past 6 months	Short-term treatment response	Negative	Impaired short-term treatment response	NA	No significant predictors	NA
Quintana et al., 2021	Mortality	Mortality	Positive	Reduced chance of mortality	NA	No significant predictors	NA
Quintana et al., 2021	Mortality	Mortality	Negative	Increased chance of mortality	Older age (higher = increased risk of mortality)	Advanced age at diagnosis	Age
Quintana et al., 2021	Mortality	Mortality	Negative	Increased chance of mortality	Tumor-related etiology (yes = increased risk of mortality)	Tumor-related etiology	Diagnosis
Quintana et al., 2021	Mortality	Mortality	Negative	Increased chance of mortality	Generalized seizures (yes = increased risk of mortality)	Presence of GTCS	Seizure characteristics/types
Sharma et al., 2021	12-month seizure remission	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Sharma et al., 2021	12-month seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	NA	No significant predictors	NA
Sharma et al., 2021	Seizure recurrence	Seizure remission	Positive	Increased chance of seizure remission	NA	No significant predictors	NA
Sharma et al., 2021	Seizure recurrence	Seizure remission	Negative	Reduced chance of seizure remission	Epileptogenic neuroimaging findings (yes = higher rate of seizure recurrence)	Presence of epileptogenic lesion	Neuroimaging
Sharma et al., 2021	Seizure recurrence	Seizure remission	Negative	Reduced chance of seizure remission	Prediagnosis seizure number (5+ = higher rate of seizure recurrence)	Higher pretreatment seizure count	Seizure characteristics/types
Sharma et al., 2021	Seizure recurrence	Seizure remission	Negative	Reduced chance of seizure remission	Treatment approach (deferred = higher rate of seizure recurrence)	Delayed treatment onset	Response
Sillanpää and Shinnar, 2002	5-year terminal seizure remission	Seizure remission	Positive	Increased chance of seizure remission	Response (early = increased probability of remission)	Early response	Response
Sillanpää and Shinnar, 2002	5-year terminal seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	Seizure type (partial or atonic = decreased probability of remission)	Partial or atonic seizures	Seizure characteristics/types
Sillanpää and Shinnar, 2002	5-year terminal seizure remission	Seizure remission	Negative	Reduced chance of seizure remission	Status epilepticus (occurrence = lower rate of remission)	Status epilepticus	Seizure characteristics/types

(Continues)

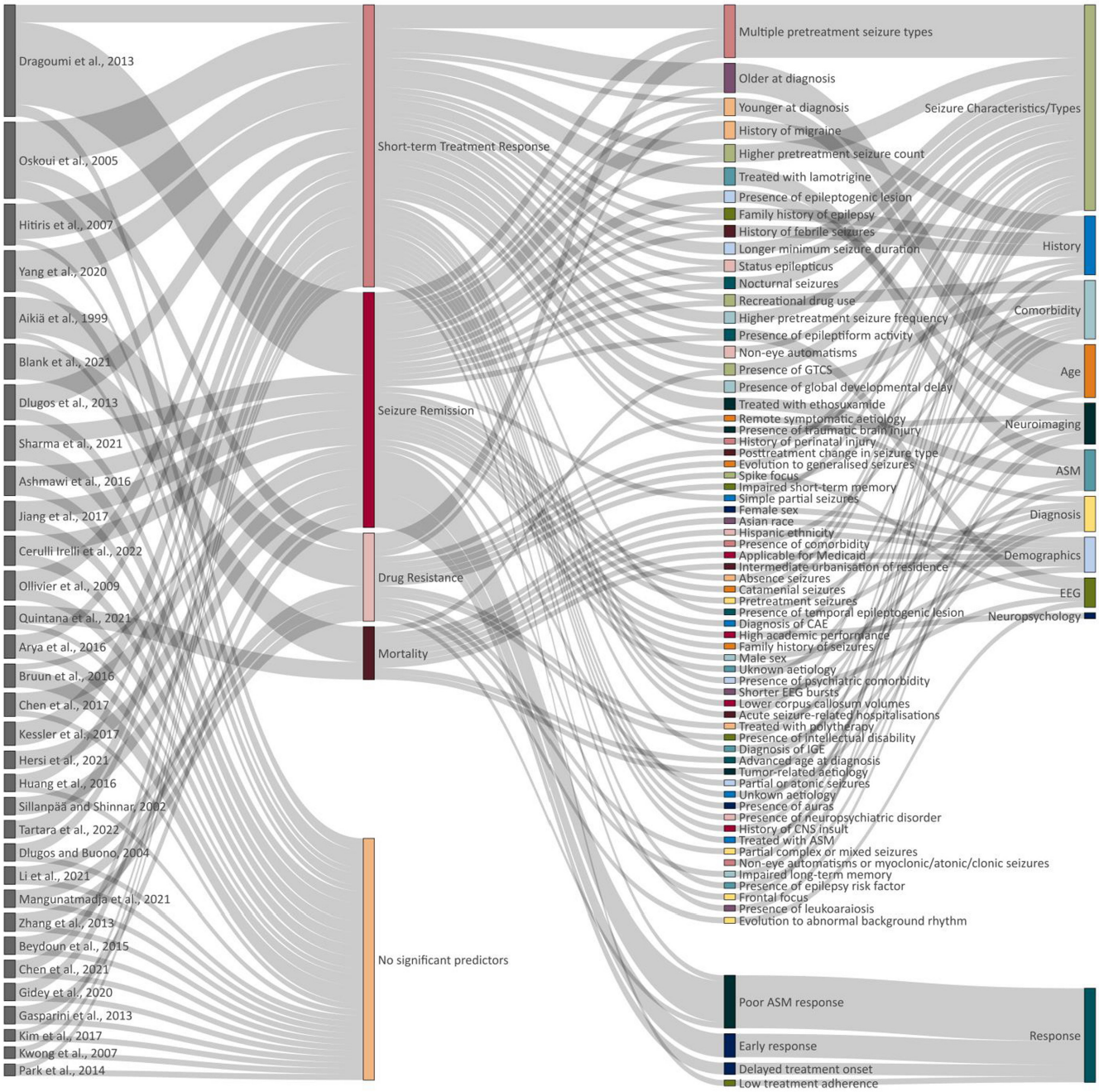
APPENDIX C (Continued)

Citation	Outcome: verbatim	Outcome: category	Outcome: valence	Outcome: operationalized	Predictor: verbatim	Predictor: general	Predictor: category
Tartara et al., 2022	Seizure freedom	Short-term treatment response	Positive	Improved short-term treatment response	Etiology (unknown = lower risk of recurrence)	Unknown etiology	Diagnosis
Tartara et al., 2022	Seizure freedom	Short-term treatment response	Negative	Impaired short-term treatment response	Subjective perceptions at seizure onset (presence = higher risk of recurrence)	Presence of auras	Seizure characteristics/types
Tartara et al., 2022	Seizure freedom	Short-term treatment response	Negative	Impaired short-term treatment response	Leukoaraiosis (presence = higher risk of recurrence)	Presence of leukoaraiosis	Neuroimaging
Yang et al., 2020	Seizure freedom at 12 months	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Yang et al., 2020	Seizure freedom at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Circadian rhythm (seizures in wake and sleep = poor probability of seizure freedom)	Nocturnal seizures	Seizure characteristics/types
Yang et al., 2020	Seizure freedom at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Pre-ASM EEG (epileptiform discharges = poor probability of seizure freedom)	Presence of epileptiform activity	EEG
Yang et al., 2020	Seizure freedom at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Neuropsychiatric disorder (presence of any = poor probability of seizure freedom)	Presence of neuropsychiatric disorder	Comorbidity
Yang et al., 2020	Seizure freedom at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	Perinatal brain injury (yes = poor probability of seizure freedom)	History of perinatal injury	History
Yang et al., 2020	Seizure freedom at 12 months	Short-term treatment response	Negative	Impaired short-term treatment response	History of CNS infection (yes = poor probability of seizure freedom)	History of CNS insult	History
Yang et al., 2020	Seizure freedom at 6 months	Short-term treatment response	Positive	Improved short-term treatment response	NA	No significant predictors	NA
Zhang et al., 2013	Poor outcome	Drug resistance	Positive	Reduced chance of drug resistance	NA	No significant predictors	NA
Zhang et al., 2013	Poor outcome	Drug resistance	Negative	Increased chance of drug resistance	Multiple seizure types (yes = greater chance of poor outcome)	Multiple pretreatment seizure types	Seizure characteristics/types
Zhang et al., 2013	Poor outcome	Drug resistance	Negative	Increased chance of drug resistance	Changes in seizure type during treatment (yes = greater chance of poor outcome)	Posttreatment change in seizure type	Seizure characteristics/types

Abbreviations: ASM, antiseizure medication; CAE, childhood absence epilepsy; CBZ, carbamazepine; CNS, central nervous system; EEG, electroencephalogram; ETX, ethosuximide; GTCS, generalized tonic–clonic seizures; IGE, idiopathic generalized epilepsy; LOC, loss of consciousness; LTG, lamotrigine; NA, not available; VPA, valproate.

APPENDIX D

Sankey diagram showing studies and predictors, grouped by outcomes.[10,26,29,47–75]



Abbreviations: ASM, antiseizure medication; CAE, childhood absence epilepsy; CNS, central nervous system; EEG, electroencephalography; GTCS, generalized tonic–clonic seizures; IGE, idiopathic generalized epilepsy.

APPENDIX E

Descriptive summary of included machine learning-based prediction models in newly diagnosed epilepsy.[81–83]

Citation	PWE, *n*	Epilepsy diagnosis	Patient age, years (SD)	Outcomes	Outcome time points	Modeling method	Development/ test	Model predictors
Croce et al., 2021	32	Temporal lobe epilepsy	50.00 (22.30)	Seizure freedom	2 years	Partial least squares regression with leave-one-out cross-validation	72/28	Pretreatment EEG Posttreatment EEG (3 months)
Lee et al., 2021	160	Focal epilepsy	39.50 (19.40)	ASM response	>1 year	Support vector machine	80/20	Age Sex Age at onset Prediagnostic duration Prediagnostic seizure frequency Pretreatment EEG Neuroimaging abnormalities Diffusion tensor parameters Connectomic parameters
Hakeem et al., 2022	1798	NS	34.00 (24.00–50.00)[a]	Seizure freedom	1 year	Attention-based transformer model	80/20	Sex Age at treatment initiation Clinical history Presence of comorbidity Pretreatment seizure number Diagnosis Pretreatment EEG Neuroimaging abnormality ASM

Abbreviations: ASM, antiseizure medication; EEG, electroencephalogram.

[a]Median (range).