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Predictive model for initial response to first-line treatment in children with infantile epileptic spasms syndrome

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Abstract

Background Previous studies have suggested that factors such as the treatment interval and aetiology may influence the initial response rate to first-line treatment for infantile epileptic spasms syndrome (IESS). However, few children with IECSS have undergone clinically accessible tests to determine the aetiology.

Methods Using a dataset from our previously published research, we constructed and tested a predictive model for the initial response to first-line treatment in children with IESS. Random sampling and 5-fold cross-validation were performed, with synthetic minority oversampling technique to correct data imbalance. Machine learning algorithms and evaluation metrics optimised model accuracy and efficacy.

Results This study included 532 children with IESS who had completed monotherapy first-line treatment, of whom 160 achieved an initial response. The model's accuracy, F1 score, and area under the curve (AUC) in the validation set were 0.7836 ± 0.0229 (ranging from 0.75167 to 0.80536), 0.7833 ± 0.0229 (ranging from 0.75145 to 0.80531), and 0.8516 ± 0.0165 (ranging from 0.82468 to 0.86936), respectively. Factors such as the age of seizure onset, age of spasm onset, lead time, MRI subtype, treatment choice, and age at treatment consistently ranked in the top six for importance in contributing to the model.

Conclusions The study findings suggest that this model may help effectively predict the initial response to first-line treatment, supporting clinical decision-making for children with IESS. Key predictors such as the age of seizure onset and MRI subtype enable early, data-driven intervention strategies in clinical practice.

Keywords Infantile epileptic spasms syndrome (IESS), First-line treatment, Initial response, Predictive model

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Introduction

Infantile epileptic spasms syndrome (IESS), formerly known as infantile spasms or West syndrome, is an age-dependent epileptic encephalopathy characterised by the occurrence of epileptic spasms. The onset of IESS typically manifests within the first year postnatally, although the presentation may sometimes be delayed up to 24 months. Recent studies have highlighted that IESS is among the most prevalent epileptic encephalopathies of early childhood. For example, according to the findings of Coryell et al., over one-third of patients with epilepsy aged under three years are diagnosed with IESS [1]. Furthermore, Jonsson et al. reported that 50% of infants who developed epilepsy within the first year of life later developed IESS [2]. Most children affected by IESS experience residual cognitive deficits, underscoring the potential benefits of prompt intervention and spasm control for improved neurodevelopmental outcomes.

The initial efficacy of treatments for IESS varies widely, ranging from 30 to 80%. However, more extensive recent studies report a modest initial efficacy of approximately 40% for IESS, with long-term outcomes closely linked to the early control of spasmodic seizures [3]. Several studies have employed analytical techniques on raw electroencephalogram (EEG) data to identify predictors of treatment efficacy for IESS. For example, our earlier research indicated that the complexity of the γ-band in occipital lobe EEG recordings exhibited optimal discriminative performance for treatment response, corresponding to an area under the receiver operating characteristic curve (AUC) of 0.8621. In contrast, the complexity of the δ-band could serve as a reasonable predictor for overall adverse outcomes [4]. Studies by Rajsekar R. Rajaraman and colleagues have identified entropy and long-range temporal correlations as potential initial efficacy and relapse predictors [5]. Research by Junhyung Kim et al. on 40 children with IESS suggested that the strength of functional connectivity across different regions and frequency bands via EEG could effectively predict the initial response to vigabatrin (VGB) treatment [6]. Sotaro Kanai and others proposed that pretreatment EEG features, such as the relative power spectrum (rPS), weighted phase lag index (wPLI), and graph theoretical analysis, may serve as early effective predictors of the response to adrenocorticotropic hormone (ACTH) therapy [7]. Furthermore, Ryuki Matsuura et al. reported that the serum levels of matrix metallopeptidase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) can predict the response to ACTH therapy in patients with infantile spasms [8]. Unfortunately, although these factors may hold predictive value for the efficacy of IESS treatment, such methods and observational markers are not readily accessible in clinical settings and often require engineering expertise for in-depth data processing. Additionally, only the model constructed by Yuto Arai et al. using clinical data has demonstrated high sensitivity and specificity for predicting poor seizure outcomes (86.7% and 64.3%, respectively) and poor developmental outcomes (88.9% and 100%, respectively); however, this model is based on a relatively small cohort of just over 40 patients with IESS [9].

The therapeutic principle for IESS is the early and rapid control of spasmodic seizures. Current first-line treatments for IESS include two major categories: hormonal agents and VGB [3, 10, 11]. A randomised controlled trial (RCT) conducted in 2017 confirmed that the early combination of VGB and hormonal therapy, compared with monotherapy, may significantly improve the initial control rate of IESS [12]. Recent research by Yuskaitis et al. also recommends evaluating the efficacy of a single drug as early as possible and then deciding whether to immediately add a second treatment modality [13]. However, considering the side effects of VGB [14–17], such as visual field defects, cranial MRI-related imaging abnormalities, and economic considerations, the effectiveness of combination therapy, although demonstrated, is still somewhat limited. This was particularly highlighted by Bhalla et al. in 2020, who reported three cases of severe encephalopathy in children treated with VGB, one of which resulted in death, potentially related to the combined use of hormones and VGB [18]. Therefore, early prediction of whether children with IESS will respond to monotherapy supports more informed treatment decisions, such as opting for combination therapy, which may significantly benefit the treatment of IESS. Physicians may also be able to devise more appropriate treatment plans for children with IESS at their initial consultation, aiming for the early control of spasms, especially considering the imbalance in medical resources between regions. For example, higher-income countries may have more paediatric neurologists, whereas lower-income countries may have very few [19]. Establishing such a model could help narrow the global gap in medical resources available to children with IESS.

Prior investigations have established that the latency from the onset of IESS to the initiation of therapeutic intervention is a significant determinant of both the immediate efficacy of treatment and the long-term neurodevelopmental prognosis. Our previous research revealed that a reduced lead time is associated with an increased probability of securing an initial response. However, when seizure onset precedes the age of three months, a period during which an initial response is achieved becomes notably more arduous [20]. In a study by Daida and colleagues, which assessed a cohort of 107 children with IESS of structural-acquired origin, it was posited that these patients exhibited a heightened propensity for an initial response to treatment [21].

Concurrently, Chourasia et al.'s investigation of IESS cases stemming from non-acquired aetiologies indicated that patients with recognisable dysmorphic/syndromic diagnoses were more likely to achieve a positive initial response [22]. Despite these insights, the aforementioned studies primarily delineate associative links between clinical variables and short-term treatment responses without providing a robust framework for individual patient management. The challenge persists in synthesising these variables into a cohesive model for clinical application. Developing a model that meticulously integrates these factors would be of immense value to paediatric neurologists in optimising the management of children diagnosed with IESS, ultimately enhancing patient care.

Our current research focused on constructing an initial efficacy prediction model for IESS based on data readily available in a clinical setting, such as aetiology, age at onset, and treatment interval. This study references the most extensive IESS retrospective cohort study published to date, which gathered data from exhaustive clinical examinations (since factors such as aetiology and treatment interval are closely associated with initial efficacy) [11]. Our predictive model was developed and validated based on this robust dataset.

Methods

Ethical approval

Informed consent for participation in this study was obtained from the patients' parents, and the participants did not receive the stipend. All data are de-identified and protected by privacy safeguards. Ethical approval for the study was granted by the Ethics Committee of the First Medical Centre of the PLA General Hospital (S2022-208-01).

Data source

The data for this study were sourced from our previously published research, which included a cohort of 532 children diagnosed with IESS who had completed monotherapy with first-line agents, including hormonal drugs (ACTH or prednisolone) or VGB. All 532 children underwent comprehensive clinical examinations to determine the aetiology of their condition. In this cohort, over 75% of the children had a clearly identified aetiology [20], comparable to the findings of another study in which 82% of the IESS cohort had completed exhaustive clinical examinations [22]. In our previously published cohort of 532 children who completed first-line therapy, the efficacy rate was 32%, similar to the initial efficacy rate of 33% reported by Deckard et al. in their recent study of over 300 cases of IESS [23]. Considering these two aspects, this dataset is currently the largest and most representative clinical dataset of children with IESS.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Participants

We collected clinical data from children diagnosed with IESS who visited our hospital (Beijing, China) from January 2018 to June 2023. The inclusion criteria for patients were as follows: met the diagnostic criteria for IESS as per the guidelines published by the International League Against Epilepsy (ILAE) in 2022 [24] and had completed first-line therapy [20]. Standardised treatment included the use of an adequate dose of ACTH for more than 2 weeks, VGB at a minimum dose equivalent to the recommended dose, or oral steroids at the prescribed dose for 1 month. Patients had undergone clinically available examinations to determine the aetiology. Briefly, the sequence of examinations was as follows: cranial MRI, genetic testing, and metabolic testing. All patients classified as having unclear aetiology must have completed all three examinations to be included in this study. Any data with missing information was excluded from the research.

The data collected for this study were rigorously evaluated. For all clinical data, confirmation was obtained from at least two paediatric neurologists, and in cases of disagreement, a more senior paediatric neurology specialist was consulted for final confirmation. The results of genetic testing were based on the American College of Medical Genetics and Genomics (ACMG) rating standards, and only mutations judged to be pathogenic or likely pathogenic in relation to IESS were considered to have genetic abnormalities. The radiological examination results were confirmed by radiologists. Notably, all radiological examinations deemed negative required reconfirmation by a paediatric neurologist before being considered normal. For any discrepancies, a conclusion was reached after further discussion between the paediatric neurologist and the radiologist.

Outcome

The outcome of interest in this study was the initial response of children with IESS to first-line treatment. The criteria for determining the initial response, consistent with those used by Chourasia et al. and in our previous research [20, 22], are as follows: the control of spasmodic seizures during the course of first-line treatment and the continuation of this control for at least four weeks after the end of treatment. The absence of such control is defined as a nonresponse.

Predictors

In our previous study [20], we identified a range of predictors, including sex; the type of first epileptic seizure;

the timing of the first epileptic seizure; the occurrence of epileptic seizures in early life (early-onset seizures, defined as those occurring when ≤ 3 months of age); the age at onset of spasmodic seizures; the presence of late-onset spasms (defined as those with an age > 12 months at the time of spasms); the presence of other seizure types concurrent with spasms; the presence of hypsarrhythmia; developmental delay prior to spasms; the type of first-line treatment used (including ACTH, corticosteroids, and VGB); the age at initiation of first-line treatment; abnormalities on cranial MRI; their specific classification (including normal; acquired structural abnormalities further divided into perinatal brain injury and developmental brain injury; and congenital structural abnormalities such as reduced brain volume, dysplastic brain disorders, developmental tumours, and malformations of cortical development [MCD]); and the aetiological classification of IESS (including acquired structural abnormalities, genetic abnormalities with normal structure, congenital structural abnormalities with genetic abnormalities, congenital structural abnormalities without genetic abnormalities, and unknown causes). The methods for determining these predictors and the detailed process can be found in our previous study [20]. The selection of predictors for our current study included all the features collected above, which encompass clinical characteristics related to the initial response to first-line treatment for IESS, as reported in previous research.

Sample size

We used 16 independent variables as predictive factors. Previous studies have reported that the initial efficacy rate of first-line treatment in children with IESS is approximately 40%. Thus, we set the response rate at 40%, anticipating that the model's predictive ability could achieve an AUC of 0.8. Referring to the study by Richard et al. [25], we calculated the sample sizes as 487, 367, and 369, respectively, with the final sample size determined to be 487 individuals. Our study included a cohort of 532 children with IESS, which fully met the requirements. Considering the potential need to address data imbalance further, we revised the response rate to 50%, and the calculated sample sizes were 468, 360, and 385, with the final sample size determined to be 468 individuals. The number of participants in the cohort included in this study still met the requirements.

Model construction and validation

During the construction and validation of the model, we first addressed data balance using the synthetic minority oversampling technique (SMOTE), which can balance the data between responsive and nonresponsive IESS patients. This prevents the model from excessively favouring the majority class during training and enhances its ability to identify the minority class. Next, we imputed the missing data from all medical records and re-standardised the dataset. The dataset was randomly divided into an 80% model construction set and a 20% validation set, with fivefold cross-validation conducted. In addition, we compared a variety of machine learning algorithms, including random forest. We also employed SHapley Additive exPlanations (SHAP), a methodology used to elucidate the contribution of each feature to the predictive outcomes of the model. to calculate the importance and influence direction of each predictor in the model. The detailed operational procedures can be found in the supplementary materials (Supplementary Text and Figure S1A).

Results

Participants

A total of 532 patients with IESS were included in this study, 226 (42.5%) of whom were female. One hundred and thirteen patients experienced a nonspasmodic type of seizure as their first epileptic event, with a median age at first seizure of 5.0 months (25th percentile at 3.0 months, 75th percentile at 7.1 months). Early-onset seizures were observed in 106 patients, with a median age at onset of spasmodic seizures of 5.5 months (25th percentile at 4.0 months, 75th percentile at 8.0 months). Fifty-seven (10.7%) patients were classified as having late-onset spasms, and 108 (20.3%) patients had other types of seizures concurrent with spasms. A total of 342 (64.3%) patients exhibited hypsarrhythmia during spasms and 237 (44.5%) patients experienced developmental delays prior to the onset of spasms. With respect to first-line treatment, 420 (78.9%) patients received ACTH, 51 (9.6%) received oral corticosteroids, and 61 (11.5%) received VGB. The median age at the initiation of first-line treatment was 7.5 months (25th percentile at 5.5 months, 75th percentile at 11.0 months). Abnormal cranial MRI findings were present in 354 (66.5%) patients, with 115 (21.6%) classified as having acquired structural abnormalities (including 84 (15.8%) with perinatal brain injury and 31 (5.8%) with brain injury during development) and 239 (44.9%) with congenital structural abnormalities (comprising 32 (6.0%) with reduced brain volume, 92 (17.3%) with dysplastic brain disorders, 22 (4.1%) with developmental tumours, and 92 (17.3%) with MCD). Aetiologically, 115 patients were categorised as having acquired structural abnormalities, 51 (9.6%) had genetic abnormalities with normal structure, 101 (19.0%) had congenital structural abnormalities with genetic abnormalities, 138 (25.9%) had congenital structural abnormalities without genetic abnormalities, and 127 (23.9%) had an unknown cause (see Table 1).

A total of 160 patients achieved an initial response to first-line treatment. Significant differences were observed

Table 1 532 IESS patients'demographics and inter-group analysis of response and nonresponse

Characteristic	Overall, $N=532$[1]	Nonresponse, $N=372$[1]	Response, $N=160$[1]	*p*-value
Age_of_seizure_oneset				0.018[2]
Median (IQR)	5.0 (3.0, 7.1)	5.0 (3.0, 7.0)	5.5 (4.0, 7.5)	
Age_of_spasm_oneset				0.203[2]
Median (IQR)	5.5 (4.0, 8.0)	5.0 (3.5, 8.0)	6.0 (4.5, 7.5)	
Treatment_age				0.6102
Median (IQR)	7.5 (5.5, 11.0)	7.5 (5.5, 12.0)	7.5 (6.0, 10.0)	
Lead_time				0.5092
Median (IQR)	1.50 (0.50, 3.00)	1.50 (0.50, 3.50)	1.50 (1.00, 3.00)	
Gender				0.336[3]
Male	306 (57.5%)	219 (58.9%)	87 (54.4%)	
Female	226 (42.5%)	153 (41.1%)	73 (45.6%)	
First_seizure_type				0.106[3]
Non spasm	113 (21.2%)	86 (23.1%)	27 (16.9%)	
Spasm	419 (78.8%)	286 (76.9%)	133 (83.1%)	
Onset_early				0.001[3]
≤ 3 months	106 (19.9%)	88 (23.7%)	18 (11.3%)	
˃ 3months	426 (80.1%)	284 (76.3%)	142 (88.8%)	
Spasm_late_onset				0.205[3]
≤ 12 months	475 (89.3%)	328 (88.2%)	147 (91.9%)	
>12 months and ≤ 24months	57 (10.7%)	44 (11.8%)	13 (8.1%)	
Other_type_during_spasm				0.413[3]
With other seizure type	108 (20.3%)	79 (21.2%)	29 (18.1%)	
Without other seizure type	424 (79.7%)	293 (78.8%)	131 (81.9%)	
Hypsarrhythmia				0.573[3]
No	190 (35.7%)	130 (34.9%)	60 (37.5%)	
Yes	342 (64.3%)	242 (65.1%)	100 (62.5%)	
Development_delay_prior_to_spasms_onset				0.559[3]
Yes	237 (45.0%)	169 (45.8%)	68 (43.0%)	
No	290 (55.0%)	200 (54.2%)	90 (57.0%)	
Treatment				< 0.001[3]
ACTH	420 (78.9%)	282 (75.8%)	138 (86.3%)	
Oral costeroids	51 (9.6%)	48 (12.9%)	3 (1.9%)	
VGB	61 (11.5%)	42 (11.3%)	19 (11.9%)	
MRI				0.131[3]
Abnormal	354 (66.5%)	240 (64.5%)	114 (71.3%)	
Normal	178 (33.5%)	132 (35.5%)	46 (28.8%)	
MRI_type				0.567[3]
Acquired	115 (21.6%)	74 (19.9%)	41 (25.6%)	
Congenital	239(44.9%)	194 (44.6%)	81 (45.6%)	
Normal	178 (33.5%)	103 (35.5%)	46 (28.8%)	
MRI_subtype				0.147[3]
Perinatal acquired brain injury	84 (15.8%)	51 (13.7%)	33 (20.6%)	
Postnatal acquired brain injury	31 (5.8%)	23 (6.2%)	8 (5.0%)	
Developmental tumor	22 (4.1%)	12 (3.2%)	10 (6.3%)	
Normal	178 (33.5%)	132 (35.5%)	46 (28.8%)	
MCD	93 (17.5%)	62 (16.7%)	31 (19.4%)	
Volume Loss	32 (6.0%)	25 (6.7%)	7 (4.4%)	
DBD	92 (17.3%)	67 (18.0%)	25 (15.6%)	
IESS Classification				0.078[3]
Acquired structural abnormalities	115 (21.6%)	74 (19.9%)	41 (25.6%)	
Congenital structural abnormalities with positive genetic finding	101 (19.0%)	77 (20.7%)	24 (15.0%)	
Normal structure with positive genetic finding	51 (9.6%)	41 (11.0%)	10 (6.3%)	

Table 1 (continued)

Characteristic	Overall, $N=532$[1]	Nonresponse, $N=372$[1]	Response, $N=160$[1]	*p*-value
Congenital structural abnormalities without positive genetic finding	138 (25.9%)	89 (23.9%)	49 (30.6%)	
Unknown	127 (23.9%)	91 (24.5%)	36 (22.5%)	

[1]n (%)

[2]Wilcoxon rank sum test

[3]Pearson's Chi-squared test

between the response and nonresponse groups in terms of age at first seizure, presence of early-onset seizures, and choice of first-line treatment. In contrast, other predictive factors did not significantly differ (see Table 1).

After balancing with SMOTE, both the response and nonresponse groups comprised 372 patients each, totalling 744 patients. The original dataset formed three clusters of varying densities in the t-SNE cluster plot, each containing points labelled 0 (nonresponse) and 1 (response). The two categories were mixed within the clusters, suggesting a lack of strong separation between them. The number of labels in each cluster was relatively balanced. After further balancing with the SMOTE algorithm, the new synthetic data still presented three clusters, similar to the original t-SNE clustering results, indicating that the synthetic data did not disrupt the original data distribution (see Fig. 1).

Model specification and performance

During the fivefold cross-validation process, each model-building and validation iteration included 297 and 298 individuals in the nonresponse group and 75 and 74 individuals in the response group, respectively. Across the five validation sets, the accuracy, F1 score, and AUC were 0.783 ± 0.0229 (ranging from 0.75167 to 0.80536), 0.7833 ± 0.0229 (ranging from 0.75145 to 0.80531), and 0.8516 ± 0.0165 (ranging from 0.82468 to 0.86936), respectively (see Table 2). Compared with other models (whose performance on the validation set can be found in Supplementary Table 1), our XGBoost model demonstrated the highest accuracy and F1 score (see Table 3). The AUC value during the five validation processes was 0.8516 ± 0.0165 (ranging from 0.82468 to 0.86936), which, compared with other models (the results of the fivefold cross-validation for other models can be seen in Supplementary Figure S2), indicated that the performance of our XGBoost model was similar to that of the best-performing models, with a mean AUC above 0.85 (mean AUC = 0.8544, 95% CI: 0.8516 to 0.8555) (see Fig. 2).

Interpretability

Throughout the fivefold cross-validation of our XGBoost model, the predictive factors with a mean SHAP value greater than 0.2 consistently appeared in the top six rankings. These factors were the age of seizure onset, age of spasm onset, lead time, MRI subtype, treatment, and treatment age. These six factors significantly contributed to the model (see Fig. 3 and Supplementary Table 2).

Discussion

The treatment of IESS remains challenging, and the initial response to therapy is a concern for many clinicians and researchers [11, 26, 27]. Our study suggests that predictions regarding the response to first-line treatment may be possible using clinically available data. Unlike previous studies, all the predictive factors used in our study are readily obtainable in a clinical setting and do not require further processing. This makes our model accessible and convenient for clinical application. The top six predictive factors in our predictive model contributed significantly to the overall model.

Previous extensive research has emphasised the importance of lead time for the initial response in children with IESS, with those receiving earlier first-line treatment being more likely to achieve an initial response and better developmental outcomes [12, 28–30]. Our prior research based on the data from this study has already shown a significant relationship between lead time and initial response, where a shorter lead time is more likely to result in an initial response [20]. This finding is consistent with the results of our current study, where the lead time significantly contributed to our model for predicting the initial response.

In childhood epilepsy, an earlier age of onset may indicate a greater likelihood of epileptic syndromes, developmental epileptic encephalopathies, and poor prognosis. For example, early infantile developmental encephalopathy (EIDEE), previously known as Ohtahara syndrome, begins early in life and may transition to IESS and later evolve into Lennox-Gastaut syndrome (LGS). Seizures in children with this type of epileptic syndrome are often challenging to control [24]. In our study, the group analysis results revealed that children with an earlier onset of seizures were less likely to achieve an initial response. Therefore, the age of seizure onset may have predictive value for the initial response. Previous studies have also indicated that the age of onset of spasms is associated with a lower likelihood of achieving an initial response [31, 32]. Unlike the age of first seizure, later onset of spasms, such as those occurring after 12 months of age, typically indicates a lower probability of achieving an initial response. The age at treatment is related to the age of

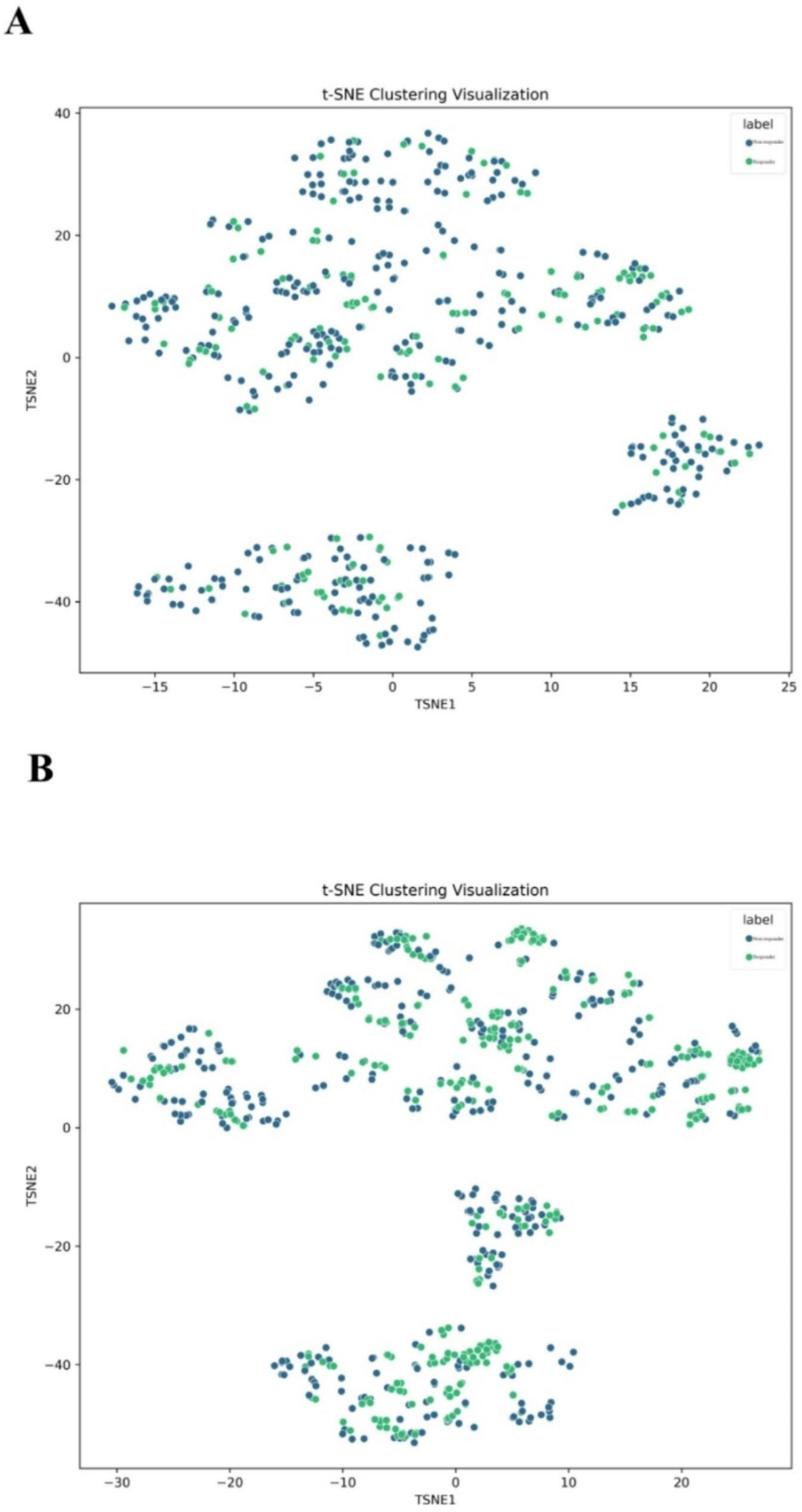

Fig. 1 T-SNE clustering visualization of original and SMOTE-enhanced data. **A**. T-SNE clustering visualisation of the original data. **B**. T-SNE clustering visualisation of the data after the SMOTE algorithm. Each point represents a patient, with blue indicating nonresponders and green indicating responders. The similar distribution intervals of responders and nonresponders confirm that there is no significant change in the data distribution after SMOTE compared with the original data distribution

Table 2 Performance of the XGBoost predictive model in the validation set during 5-fold cross-validation. AUC, area under the curve; CI, confidence interval

fold	accuracy	f1-score	AUC	AUC 95%CI lower	AUC 95%CI upper	confusion_matrix
1	0.77181	0.77160	0.85441	0.85159	0.85552	[[60 15] [19 55]]
2	0.80536	0.80531	0.86936	0.86653	0.87031	[[59 16] [13 61]]
3	0.80536	0.80473	0.85810	0.85758	0.86153	[[64 10] [19 56]]
4	0.75167	0.75145	0.82468	0.82268	0.82681	[[58 16] [21 54]]
5	0.78378	0.78342	0.85153	0.84996	0.85385	[[61 13] [19 55]]
Average	0.7836 ± 0.0229	0.7833 ± 0.0229				

Table 3 Performance comparison of the XGBoost predictive model with other models

	Accuracy	F1-score
Random Forest	0.7715 ± 0.0287	0.7714 ± 0.0288
Gradient Boosting	0.7594 ± 0.0215	0.7592 ± 0.0218
Logistic Regression	0.6317 ± 0.0225	0.6266 ± 0.0209
SVM	0.7056 ± 0.0344	0.7023 ± 0.0374
KNN	0.6788 ± 0.0346	0.6706 ± 0.0372
Decision Tree	0.6814 ± 0.0376	0.6812 ± 0.0375
Naive Bayes	0.6371 ± 0.0271	0.6339 ± 0.0288
MLP	0.7030 ± 0.0259	0.7024 ± 0.0265
LightGBM	0.7648 ± 0.0237	0.7645 ± 0.0239
OUR Xgboost	0.7836 ± 0.0229	0.7833 ± 0.0229

spasm onset and the lead time to treatment, so, understandably, this factor would make a high contribution to the model.

Research has indicated that the aetiology of IESS may be related to prognosis, with patients of unknown cause (without cranial MRI abnormalities) being more likely to achieve an initial response [11, 21]. Daida et al. suggested that patients with structurally acquired aetiology respond better to ACTH treatment than those with combined congenital aetiologies [21]. Moreover, it has long been established that patients with MCD have epilepsy that is more difficult to control [33, 34]. In our study, 87% of patients with a definite aetiology had cranial MRI abnormalities, indicating that MRI findings are related to aetiological classification and initial response and that they contributed significantly to our model.

The treatment choice was the last factor that significantly contributed to our model. Currently, first-line treatments for IESS include two major categories: corticosteroid drugs and VGB [24]. Past studies have shown that for patients with tuberous sclerosis complex (TSC) associated with IESS, VGB may be more effective than it is for IESS caused by other aetiologies. For other causes, corticosteroid drugs should be the first-line treatment of choice [3, 10, 24]. In our study, some patients had TSC associated with IESS, which explains why the treatment choice had a significant impact.

The treatment of infantile epileptic spasms syndrome (IESS) remains a challenge, and based on current therapeutic principles, early administration of effective standard treatments is of paramount importance. Although it is widely believed that initiating combination therapy from the outset may increase the short-term response rate in IESS [12], Yuskaitis and colleagues hold a differing view. Their findings suggest that early assessment of the monotherapy response followed by a decision on combination therapy might be more ideal [13]. Given the global disparity in medical resources, many regions still have limited experience diagnosing and treating IESS [19, 35, 36]. The model generated by our study can predict the likelihood of an individual IESS patient's response to monotherapy, thereby facilitating the selection of medications that are more likely to yield a short-term response and determining whether to employ combination therapy early on.

Notably, for patients with refractory spasms, surgery is an option that should be considered and has been proven effective in nearly 70% of patients with epileptic spasms [37]. Patients predicted by the model to be unlikely to respond to various first-line treatments might also benefit from this model by advancing to the presurgical evaluation stage sooner, thereby reducing unnecessary medical procedures and financial burdens. The long-term neurodevelopmental outcomes for children with IESS are linked to the control of epileptic spasms, and early control of these spasms may contribute to better long-term outcomes [3]. Our newly developed model could assist in selecting treatment strategies for children with IESS, aiming for early control of spasms and potentially improving long-term neurodevelopmental outcomes.

Limitations of the study

First, this is a secondary analysis based on our previously published research; therefore, as with prior studies, our limitations include the following points: (1) Inherent

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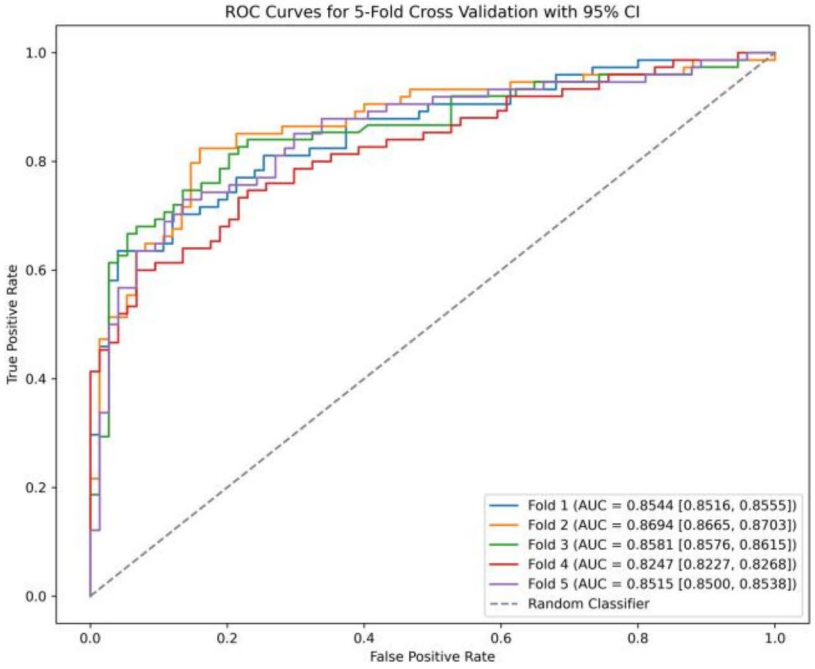

B

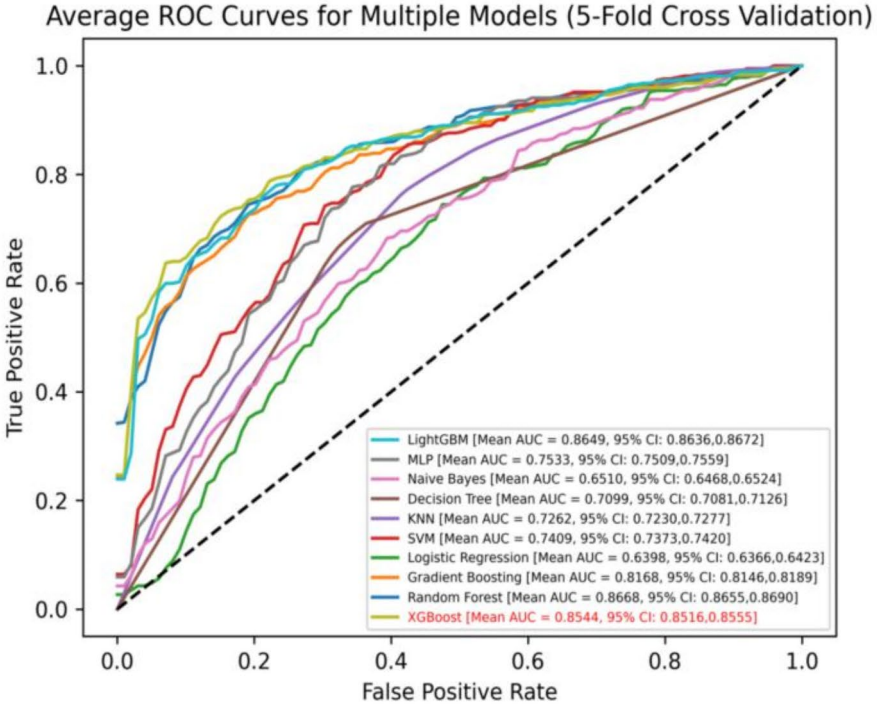

Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Performance of the XGBoost predictive model in the validation set. (**A**) AUC across 5-fold cross-validation, each color represents each fold; (**B**) AUC (mean value of 5-flod) comparison with other models, each color represents a different model, and all AUC values are the v of the 5 - fold of a single model. The multiple coloured curves represent the results of fivefold cross-validation, illustrating the relationship between the true positive rate (TPR) and the false-positive rate (FPR) at different thresholds. The closer the curve is to the top left corner, the better the model's performance; AUC, the area under the curve, is a critical metric for measuring model performance. Values closer to 1 indicate better classification performance; CI, confidence interval, provides a potential range for the AUC value. At a certain confidence level, there is a high probability that the actual AUC value will fall within this interval, helping to assess the uncertainty in the model's performance

biases are associated with the retrospective nature of the analysis; selection bias is an inevitable issue, and confounding bias may also arise from factors that were not measured. Additionally, the potential for information bias exists owing to the variability in how different physicians document within medical record systems; (2) Some patients sought secondary treatment at our centre after failing treatment at other hospitals (these patients had a significantly reduced initial response rate because they only sought secondary treatment at our centre after treatment failure or relapse elsewhere); (3) The number of patients treated with VGB was small, and the data between patients treated with hormonal medications may not be sufficiently balanced, which could lead to measurement or model evaluation bias during the analysis process. This may challenge the generalisability of the model in our study results. However, as previously mentioned, VGB is not the first choice for non-TSC-related IESS patients, so this issue seems unavoidable in real-world research. In summary, given these limitations, caution is warranted when interpreting the results of our predictive model. Further validation with other studies may help test the capabilities of our predictive model.

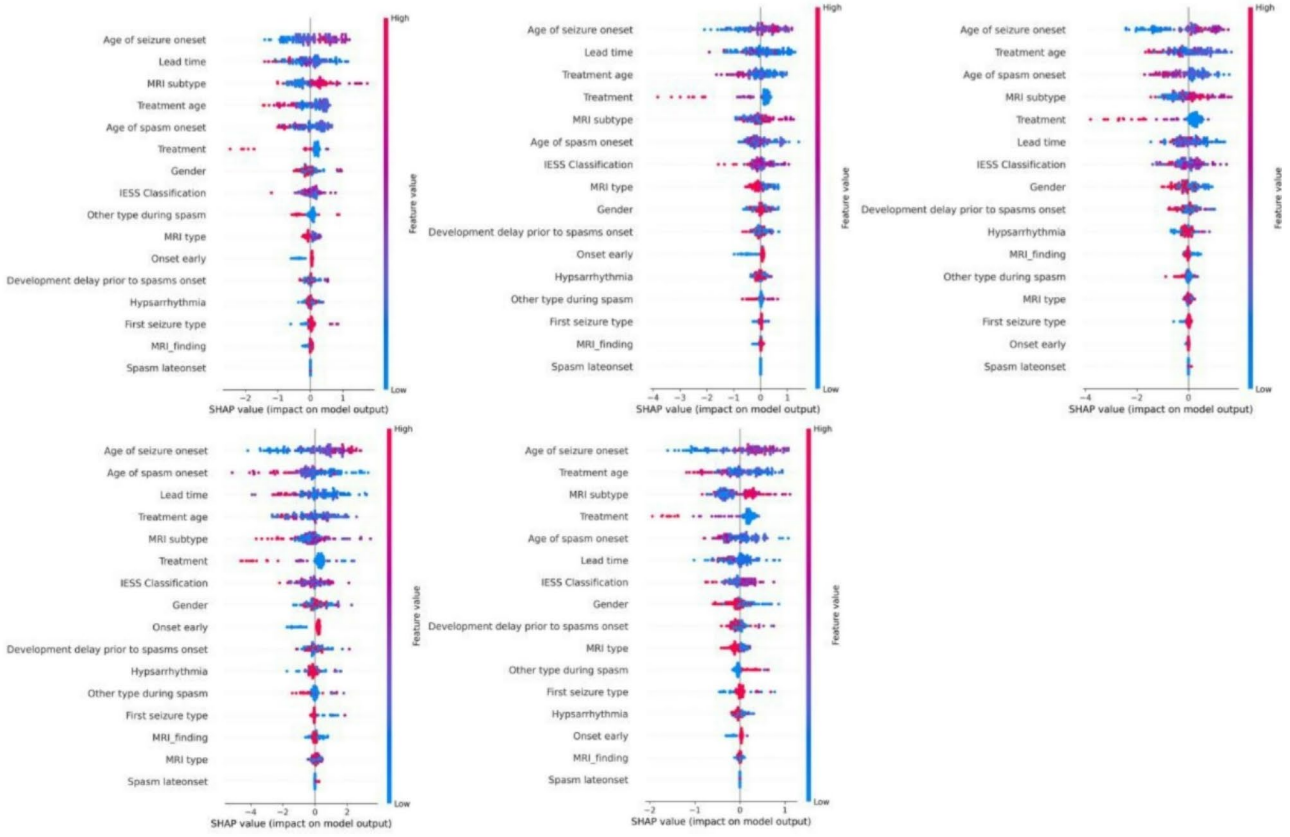

Fig. 3 Interpretability of predictors in the XGBoost predictive model during 5-fold cross-validation. The vertical axis lists a series of features arranged by the average magnitude of their SHAP values. The horizontal axis represents the SHAP value for each feature, indicating the impact of each feature on the model's prediction. Larger absolute SHAP values indicate a more significant effect. Points represent the SHAP values for individual samples across features. Point position corresponds to the SHAP value on the horizontal axis and the feature on the vertical axis. The colour of the points indicates the impact level: red signifies a high impact (High), meaning that the feature significantly increases the model's output or response rate; blue represents a low impact (Low), meaning that the feature significantly decreases the model's output or response rate. This visualisation helps identify which features most influence the model's predictions and how different feature values (high or low) affect individual predictions. It provides an intuitive understanding of the model's behaviour, facilitating stakeholder communication

Conclusions

We developed a predictive model based on clinically available data that has demonstrated a reasonable level of predictive ability. All predictive factors in this model can be obtained in clinical practice without secondary processing. This allows paediatric neurologists to predict the effectiveness of first-line treatment responses in children with infantile epileptic spasms syndrome (IESS) using our model and to plan or adjust treatment plans accordingly, such as incorporating a second first-line treatment drug earlier. In the future, we plan to increase the sample size further and update the corresponding model versions. We aim to develop this model into an installable software tool that, upon completing the necessary examinations, can automatically recommend a treatment plan for each child with IESS based on their electronic health records. Details of this hypothetical operational mode can be found in the supplementary materials (Fig. S1B). We are also working to invite more researchers from other centres to validate the predictive ability of our model. Simultaneously, we are keen to refine the model further based on the feedback from researchers at different centres.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13052-025-01959-z.

Supplementary Material 1

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Author contributions

Ge W, Wan L, and Wang Z wrote the first draft of the manuscript. Wan L and Yang G acquired the data. Wan L and Wang Z performed the data analyses. Yang G and Fu L contributed to the conception and design of the study. All authors helped to revise the manuscript regarding important intellectual content. All authors approved the final version for publication.

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Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate

Informed consent for participation in this study was obtained from the patient's parents. Data are deidentified and protected by privacy safeguards. Ethical approval for the study was granted by the Ethics Committee of the First Medical Centre of the PLA General Hospital (S2020-337-01).

Consent for publication

Written informed consent was obtained from the parents of the enrolled children.

Competing interests

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. 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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