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Epilepsy diagnosis using a clinical decision tool and artificially intelligent electroencephalography

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Abstract

Objective: To construct a tool for non-experts to calculate the probability of epilepsy based on easily obtained clinical information combined with an artificial intelligence readout of the electroencephalogram (AI-EEG).

Materials and Methods: We performed a chart review of 205 consecutive patients aged 18 years or older who underwent routine EEG. We created a point system to calculate the pre-EEG probability of epilepsy in a pilot study cohort. We also computed a post-test probability based on AI-EEG results.

Results: One hundred and four (50.7%) patients were female, the mean age was 46 years, and 110 (53.7%) were diagnosed with epilepsy. Findings favoring epilepsy included developmental delay (12.6% vs 1.1%), prior neurological injury (51.4% vs 30.9%), childhood febrile seizures (4.6% vs 0.0%), postictal confusion (43.6% vs 20.0%), and witnessed convulsions (63.6% vs 21.1%); findings favoring alternative diagnoses were lightheadedness (3.6% vs 15.8%) or onset after prolonged sitting or standing (0.9% vs 7.4%). The final point system included 6 predictors: Presyncope (−3 points), cardiac history (−1), convulsion or forced head turn (+3), neurological disease history (+2), multiple prior spells (+1), postictal confusion (+2). Total scores of ≤1 point predicted <5% probability of epilepsy, while cumulative scores ≥7 predicted >95%. The model showed excellent discrimination (AUROC: 0.86). A positive AI-EEG substantially increases the probability of epilepsy. The impact is greatest when the pre-EEG probability is near 30%.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2023.109135.

Significance: A decision tool using a small number of historical clinical features accurately predicts the probability of epilepsy. In indeterminate cases, AI-assisted EEG helps resolve uncertainty. This tool holds promise for use by healthcare workers without specialty epilepsy training if validated in an independent cohort.

Keywords

Epilepsy; Diagnosis; EEG; Decision too

1. Introduction

Establishing the diagnosis of epilepsy in a patient who presents with complaints of paroxysmal seizure-like events can be challenging. The process starts with obtaining a thorough patient history and, if resources permit, additional testing such as an electroencephalogram (EEG) and a brain imaging study. A substantial subset of people with epilepsy (PWE) is misdiagnosed for many years [1–4]. This is the case even if patients first see an epilepsy specialist [5,6]. There are multiple reasons for this. First, there is a staggering shortage of neurologic expertise globally, which is projected to worsen in both high and lower-middle-income countries (LMIC) as the prevalence of neurologic disease increases [7,8]. This lack of available expertise to diagnose epilepsy is an issue that is of urgent public health interest, given that PWE comprise approximately 1% of the world's population, and that a significant amount of morbidity and mortality of epilepsy can be mitigated by preventing seizures through cost-effective medicines [9–11]. The World Health Organization (WHO) recently stated in its global action plan a goal to expand preventative, diagnostic, and treatment options for PWE [12]. Second, the diagnosis of patients with paroxysmal seizure-like events is difficult because of the wide variety of conditions in the differential diagnosis list, including the various types of syncope, transient ischemic attacks, movement disorders, sleep disorders, atypical migraine, and psychiatric conditions. Third is that the misinterpretation of normal EEGs, in which normal EEG variants are incorrectly labeled as epileptiform discharges, is common [1–3,13,14].

An approach to solving this problem is to develop methods to enable non-experts to diagnose epilepsy. Well-calibrated decision tools allow experts and non-experts alike to minimize the well-demonstrated chance variability and biases associated with clinical decision-making [15]. The objective of the present study was to construct a decision tool that accurately predicts an epilepsy diagnosis using easily obtained clinical information, combined with information from automated EEG interpretation. The interictal EEG interpreted using artificial intelligence (AI-EEG) has recently been demonstrated to perform with greater accuracy, on average, than a group of clinical experts with subspecialty training in clinical neurophysiology [16]. We hypothesized that a point score using clinical factors alone would provide reasonable sensitivity and specificity in detecting epilepsy and that the addition of AI-EEG would further improve the diagnostic prediction.

2. Materials and methods

The study was approved by the Massachusetts General Hospital (MGH) Institutional Review Board (IRB). Two physicians (MAA, RPM) completed a retrospective chart review of 205 consecutive patients aged 18 years or older with routine EEG data from the MGH performed between April 2016, and July 2019. Data collection occurred in 2020–2021, the minimum follow-up period was one year, and most patients had more than 2 years of follow-up. Patients were excluded in a consecutive manner if the index EEG was associated with admission to a medical intensive care unit, if the ultimate diagnosis was determined to be a toxic-metabolic encephalopathy due to a medical cause, if the reason prompting the EEG could not be determined, or if the ultimate diagnosis was not documented. If the clinician documented that he or she was uncertain of the diagnosis after evaluation, it was categorized as “unknown.” Physician reviewers (AA, RM) met regularly to review data entry and ensure inter-reviewer concordance for all variables. The ultimate diagnosis was the one documented most recently in each patient’s chart. For example, if a patient first presented with loss of consciousness (LOC) thought to represent syncope, but later developed recurrent convulsions and had the diagnosis revised to epilepsy, the recorded diagnosis was epilepsy. In this way, we sought to establish a ground truth diagnosis for each patient that benefited from the availability of repeated visits over time, and any imaging or EEG testing performed, i.e., a diagnosis as accurate as can be achieved in real-world clinical practice. We aimed to develop a diagnostic approach that predicts this ground-truth diagnosis using easy-to-obtain clinical history, paired with automated EEG reading.

2.1. Variables of interest

Variables of interest included basic demographic information, indication for the index EEG, semiologic features associated with the patient’s presentation, and whether an antiepileptic medication was either recommended or prescribed. Operational definitions for select clinical variables are provided in the supplemental material.

2.2. Statistical analysis

Patients diagnosed with epilepsy were compared to those with other diagnoses using *t*-tests for means, and chi^2 tests for frequencies using RStudio software. Alpha (a) was set to 0.05.

Multivariable logistic regression was applied to quantify the probability of epilepsy using baseline clinical and demographic variables. Twenty-seven candidate features were first grouped into 15 predictors for the model (Table 1). Risk factors not explicitly mentioned in the medical record were assumed to be absent. In addition, L1 (LASSO) regularization was applied for feature selection. In this cohort, the model was trained to predict binary outcomes, i.e., Epilepsy (value 1, N+ = 110) and Non-epilepsy (value 0, N− = 95, including 52 definite, and 43 indeterminate cases).

We used 10-fold cross-validation (CV) for model testing, to obtain an unbiased estimate of model performance. For each of the 10 rounds of CV, we split the data into training (90%) and testing (10%) data. For each fold of the CV, the training data was further split into training and internal validation data (90% to 10%) to facilitate feature selection.

Models were fit for a range of L1 regularization parameter values k, and for each value, the performance was measured on the internal validation set. The global optimal was determined such that deviance was within one standard error of the value which produced the best average performance across the 10 folds. To arrive at a robust and practical decision tool, we further simplified the model by eliminating predictors that were selected in fewer than or equal to 20% of the training folds (<3 times out of 10 during CV). Finally, we retrained the model with the final remaining features and rounded the coefficients to arrive at an integer-coefficient model or *point system*.

To update the pre-test probability provided by the clinical history-based point system into a post-test probability informed by AI-EEG findings, we trained a second logistic regression model. This model combines the result of the point system described above with a single value provided by the AI-EEG algorithm, which can be either 1 = “positive” or 0 = “negative”. This binary value is obtained by taking the probability that an EEG contains epilepti-form discharges, determined by a previously described deep neural network (SpikeNet), and comparing this probability to a threshold [16]. We chose this threshold as the value which maximizes the positive likelihood ratio for epilepsy, LR+ = Sensitivity / (1-Specificity).

2.3. Rationale for study size

We considered the minimum clinically meaningful area under the curve (AUC) to be 0.75; we thus set our null hypothesis to be H0: AUC <= 0.75. For the alternative hypothesis, we reviewed the prior literature and found that in the prior manuscript most similar to ours, clinical features were able to separate syncope from seizures with an AUC of >0.95. was 0.85 [17]. Because our cohort was more diverse than that of the cohort in reference, we assumed that the best achievable AUC would be somewhat lower, therefore we set as our alternative hypothesis H1: AUC > 0.85. From these assumptions, we calculated that a sample of 95 from the epilepsy group and 95 from the non-epilepsy group would provide 80% power to detect a difference of at least 0.08 between the AUC under the null vs alternative hypotheses. These calculations were done using a one-sided z-test at a significance level of 0.05, assuming continuous responses with false positive rates between 0 and 1, and the ratio of the standard in responses in the negative group to the standard deviation of the responses in the positive group as 1.

3. Results

Of 205 patients, 104 (50.7%) were female, the mean age was 46.04 years, and 110 (53.7%) ultimately were diagnosed with epilepsy. Among the remaining 95 (46.3%) patients, the following final diagnoses were obtained, in order of frequency: undetermined (21%), syncope (7.8%), migraine or headache disorder (5.4%), single unprovoked seizure (3.9%), psychiatric or functional neurologic disorder (2.9%), provoked seizure (1%), stroke or transient ischemic attack (TIA) (1.5%), autonomic disorder (1%), and other miscellaneous diagnoses (2%). Among the 43 patients who had an indeter minate diagnosis, 10 (23.3%) were prescribed or recommended an anti-seizure medication.

Most index EEGs (44%) were performed on a patient with an established diagnosis of epilepsy for various reasons. In the remaining cases, reasons for performing the index EEG, in order of frequency, included: LOC (24.9%), “spells” without LOC (16.6%), and altered mental status (14.2%).

We compared patients who received a diagnosis of epilepsy to those who received other diagnoses. Epilepsy patients differed by the prevalence of developmental delay (12.6% vs 1.06%, $p = 0.0006$), history of previous neurological injury (51.4% vs 30.9%, $p = 0.006$), history of febrile seizures in childhood (4.55% vs 0%, $p = 0.02679$), postictal confusion (43.6% vs 20.0% y, $p < 0.001$), presence of a witnessed convulsion (63.6% vs 21.1%, $p < 0.001$), preceding lightheadedness (3.6% vs 15.8%, $p = 0.002$) and whether the event occurred after prolonged sitting or standing (0.9% vs 7.4%, $p = 0.014$). Univariate comparisons are summarized in Table 2.

Training the predictive model yielded 6 features that were included in the final predictive model. These are listed in Table 3 along with the number of training folds in which they were selected, and their univariate and positive/negative likelihood ratios. The model training procedure assigned the following integer weights to these 6 clinical predictors: Signs consistent with syncope/presyncope (−3 points), witnessed convulsion or forced head turn (+3 points), history of neurologic disease (+2 points), history of cardiac disease (−1 point), more than one prior spell (+1 point), and postictal confusion (+2 points). This point system, with scores ranging from −4 up to +8 points, and the corresponding predicted probabilities of epilepsy are shown in Table 4.

We measured model performance using the area under the receiver operating curve (AUROC), and by calculating calibration curves, and 10,000 rounds of bootstrapping were used to obtain 95% confidence bounds. Model performance is shown in Fig. 1. As shown in Fig. 1A and 1B, the AUROC is 0.86 [0.80, 0.90]. Choosing a threshold of 0.485, the model provides a sensitivity of 0.836 and a specificity of 0.716. In addition, the calibration error is 0.07 CI [0.04, 0.14], thus the model’s predicted probability of epilepsy closely matches the true proportion of patients with epilepsy.

The 3rd class of “Undetermined” cases ($n = 43$) was used to further evaluate the model. As shown in Fig. 1C, the model predicted probability for these cases lies between definite Epilepsy and definite non-Epilepsy, which aligns with the observation that, although these patients did not receive a definite diagnosis of epilepsy, they were prescribed or recommended to begin an anti-seizure medication.

Two factors, including “neurologic injury” and “abnormal ECG” might be difficult to know in settings with limited resources where imaging or ECG testing are less available, we performed a sensitivity analysis by treating these variables as unknown by setting them to zero and recalculating model performance. We found that overall AUC dropped to 0.84, a decrease of 2 percent. Thus, the model generally remains robust when these two variables are unavailable.

To evaluate the influence on AI-EEG findings, we computed preand post-EEG probabilities for each score from −3 to 8 in our cohort. As shown in Fig. 1D, a negative result does

not change the post-test probability. A positive result, however, can result in a post-test probability substantially higher than the pre-test probability. The impact is greatest when one is uncertain based on clinical information, i.e. when the pre-test probability is near 30%.

Although our cohort is not large enough for analysis of how the algorithm performs in patients who are ultimately diagnosed with different epilepsy subtypes, we performed a simple exploratory analysis in patients diagnosed with generalized genetic (idiopathic generalized) epilepsy, one of the most common general subtypes; we identified these as patients found to have generalized spike and wave discharges on at least one EEG. Among the 12 patients meeting this criterion, the median [range] pre-EEG probability of epilepsy was 87.4 [4.5, 98.1]%, and 98.9 [71.7, 99.7]% with positive EEG findings.

4. Discussion

In this study, we demonstrate that a simple inventory of clinical variables can predict a diagnosis of epilepsy with a sensitivity of 84% and specificity of 72%. In indeterminate cases, AI-EEG substantially improved the prediction of an epilepsy diagnosis. We propose that this clinical decision tool combined with AI-EEG may be useful in areas where epilepsy is underdiagnosed and under-treated, and where neurologic expertise is scarce.

Our data expand the concept that a patient's clinical factors can reliably distinguish epileptic from nonepileptic symptoms. Sheldon *et al.* examined a cohort of 571 patients with LOC for whom a diagnosis was determined after a rigorous diagnostic evaluation. A weighted point score was derived using regression analysis, which yielded a sensitivity and specificity for seizures of 92% and 83%, respectively [17]. There was substantial overlap with our decision tool with respect to factors that were positively and negatively predictive of seizures and epilepsy. However, their study aimed to differentiate the diagnosis in patients specifically presenting with LOC, developing a point score to accurately distinguish a seizure from syncope. In contrast, our study included patients presenting with a broad range of symptoms, including frank LOC in addition to varying alterations in consciousness, focal motor or sensory symptoms, and various neuropsychiatric phenomenon, among others. Thus, our decision tool may be more generalizable across epilepsy presentations, including the subset of PWE who do not present with LOC [6]. We suspect that the large range of presenting symptoms captured in our cohort in part explains the lower sensitivity and specificity of our decision tool, given the degree of similarity in component clinical variables. Importantly, the addition of AI-EEG improved the algorithm's performance and could enhance the diagnostic yield of the decision tool when patients do not present with straightforward clinical symptoms.

Our approach is novel in including AI-EEG in the diagnostic algorithm. The AI algorithm used for this purpose detects epilepti-form abnormalities in the EEG with greater accuracy, on average than a group of clinical experts with subspecialty training in clinical neurophysiology [16]. Integration of AI-EEG improves the performance of our diagnostic algorithm, and could still be used in areas with limited resources by obviating the need for an expert interpreter. The availability of EEG equipment is a potential barrier to

implementation, however, numerous point-of-care innovations have recently improved the cost and practicality of deploying EEG throughout the world [18,19].

Other diagnostic decision tools have been developed to guide care for PWE. A recent study applied a machine learning approach to train a diagnostic classifier that could reliably distinguish between epilepsy, syncope, and psychogenic, nonepileptic seizures (PNES) in patients presenting with LOC. Patients with confirmed diagnoses of epilepsy, syncope, and PNES were asked to complete questionnaires that detailed historical features, and symptoms associated with their LOC episodes. Witnesses also filled out questionnaires for a subset of cases. The cohort included 300 respondents who were divided into test and validation groups. The algorithm distinguished cases of epilepsy, syncope, and PNES with robust sensitivity (largely above 70%) and specificity (largely above 90%), which were improved with the addition of a witness report [20]. Limitations of the study included a very low responder rate of 28.2%, making it unclear whether the model would perform as well in all comers with LOC. In addition, like Sheldon *et al.*, the study focused solely on LOC, and thus this algorithm could not be applied to the subset of PWE who present with symptoms other than LOC. Another recent study aimed to develop a diagnostic decision tool that could reliably distinguish epileptic seizures from PNES based on information obtained from the initial interview. In a cohort of 1616 patients with confirmatory video-EEG monitoring, 76 features were identified from retrospective chart review, then prospectively applied to future encounters. The model discriminated between epileptic seizures and PNES with a sensitivity of 74%, and specificity of 84%, though similarly, was largely focused on LOC [21]. Our methodology complements this body of research, by broadening the focus to a wider array of symptoms, and combining it with novel AI-EEG.

There are several limitations to our study. Most importantly, this study represents a pilot analysis of a test cohort. Further validation of the algorithm is needed on an independent validation cohort, to confirm test performance. Patient diagnoses were retrospectively obtained and were based on the final clinical impression. Diagnoses were not strictly based on the fulfillment of “gold standard” diagnostic testing, such as prolonged EEG monitoring with spell capture for patients diagnosed with epilepsy, or cardiac monitoring in patients diagnosed with syncope. In many cases, however, such testing was obtained and did inform the clinician’s diagnosis. Case ascertainment, in general, was likely representative of a typical workup in a high-income setting for the patient’s presenting symptoms. Because clinical variables were abstracted from clinicians’ notes, some degree of confirmation bias could have been introduced. This possibility was tempered by the fact that only the final diagnosis was recorded, and in some cases represented a revised diagnosis based on new clinical information. The patient population in this study represented the catchment area of our academic hospital in Boston, MA, and therefore the external validity of our diagnostic algorithm to populations in other areas of the world requires additional inquiry.

Potential weaknesses of our clinical decision tool include that “neurologic injury” was defined as an existing diagnosis that would be expected to cause a structural brain abnormality, which in some patients may require brain imaging and may be difficult to obtain in settings with limited resources. However, in sensitivity analysis, we found that treating these variables as unknown (i.e., setting them to zero) does not substantially degrade

overall model performance. Another limitation is that AI-EEG is currently designed to detect only inter-ictal epileptiform discharges (IEDs). Other EEG patterns, such as focal slowing, may confer some additional diagnostic information. For scale-up, the clinical inventory used in this diagnostic algorithm must be applied by medical personnel without expertise in neurology, and this requires further testing.

5. Conclusion

In summary, we have developed a diagnostic algorithm for epilepsy that focuses primarily on clinical factors and provides a novel integration of AI-EEG. We provide evidence that this approach can be diagnostically valuable. Once validated and tested prospectively in the field, this algorithm could aid in the diagnosis of epilepsy and may hold particular value in settings where epilepsy expertise remains limited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Authors RPM, MAA, and JJ have no potential conflicts of interest. JH owns stock in Corticare, which was not related to this project. MBW is a co-founder and stock owner of Beacon Biosignals, which is unrelated to this work. He receives funding through NIH, which has supported this project. FJM receives funding from the Fondation Pierre Fabre, an organization that works to expand access to healthcare in LMIC, which is related to this current work. She receives funding from NIH, the Sumaira Foundation, Genentech, and Biogen, but these grants are unrelated to this project. She receives consulting fees from Horizon Therapeutics, Genentech, and Biogen, in a capacity unrelated to this project. She is involved in the founding of BrainCapture, a company that seeks to develop low-cost EEG for use in low-income settings. BrainCapture was not involved with this work.

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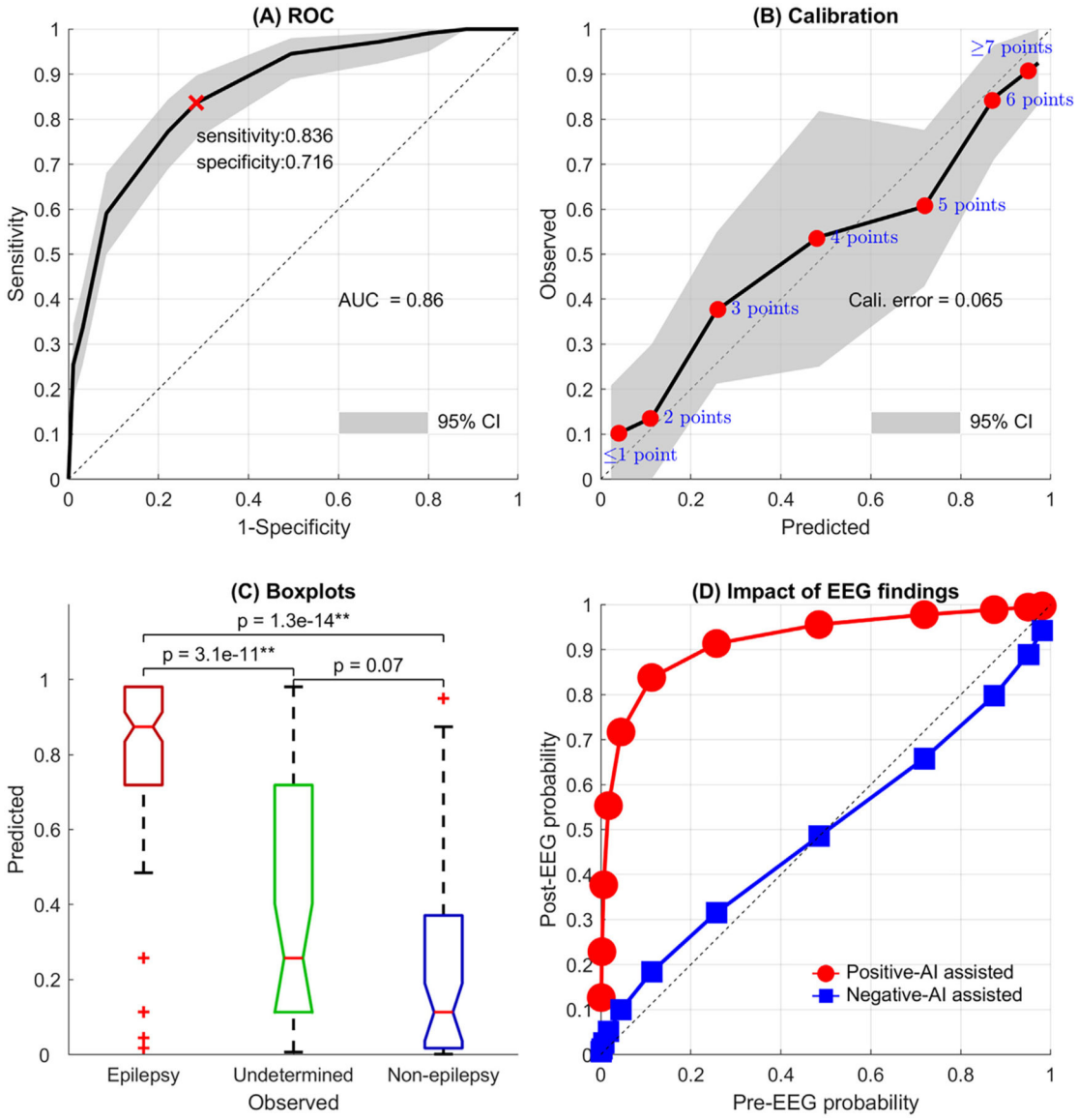

Fig. 1.

Model performance (A) ROC, (B) Calibration curve, (C) Boxplot of model prediction for each patient group, and (D) Pre- and Post-EEG probabilities with AI-assisted EEG findings added.

Table 1

List of 27 baseline clinical and demographic variables collected into 15 groups.

Syncope Signs	Black-out of vision preceding the event
	Sweating before the event
	Presyncopal lightheadedness before the event
	Event occurs after sitting or standing for a prolonged period
GTC or Forced Head Turn	Clearly described witnessed convulsion
	Head turning to one side during event
Neuro Previous Medical History	Developmental delay
	Autism
	Neurologic deficit on exam
	Previous neurologic injury
	History of neurodegenerative disease
Cardiac Previous Medical History	Abnormal ECG
	History of atrial fibrillation or flutter
	Chest pain or angina
	Dyspnea present
	Heart disease
Age	
Cyanosis observed	
Event provoked by emotional stress	
Feeling of warmth	
First-degree family history	
Number of prior spells	
Postictal confusion	
Psychiatric disease	
Substance abuse	
Tongue biting	
Urinary incontinence	

Table 2

Univariate comparison of patients who received a diagnosis of epilepsy vs other.

Demographics	Variables	Epilepsy(n = 110)	Other (n = 95)	P-Value
	Mean age in years (SD)	43.54 (20.7)	48.94 (19.5)	0.14
	Female %	47 (42.72%)	57 (60%)	**0.01**
	Right hand dominant	80 (72.73%)	54 (56.84%)	0.05
	Non-white	19 (l7.27%)	14 (14.73%)	0.35
Medical History	Psychiatric history	40 (36.36%)	36 (37.89%)	0.42
	Heart disease	7 (6.36%)	6 (6.31%)	0.42
	Substance abuse	10 (9.09%)	14 (14.73%)	0.30
	History of atrial fibrillation	1 (0.91%)	6 (6.32%)	0.10
	Number of prior spells (≥2)	80 (72.72%)	48 (50.52%)	**<0.01**
	Developmental delay	14 (12.61%)	1 (1.06%)	**<0.01**
	Previous neurologic injury	57 (51.36%)	29 (30.86%)	**0.01**
	Previous febrile seizures	5 (4.55%)	0 (0.00%)	**0.03**
	Family history of epilepsy	7 (6.36%)	6 (6.32%)	0.74
	History of neurodegenerative disease	3 (2.73%)	1 (1.06%)	0.55
	Neurological deficit on exam	29 (26.36%)	13 (13.69%)	**0.03**
	History of autism	7 (6.36%)	0 (0.00%)	**0.03**
Signs/Symptoms	**Presyncope**			
	Diaphoresis before the event	1 (0.91%)	4 (3.64%)	0.30
	Events occur after prolonged sitting or standing	1 (0.91%)	7(7.37%)	**0.01**
	Syncope			
	Dyspnea	1 (0.91%)	6 (6.32%)	0.10
	Chest pain or angina	0 (0.00%)	3 (3.16%)	0.12
	Abnormal ECG	5 (4.55%)	10 (10.52%)	0.57
	Event provoked by emotional stress	10 (9.09%)	12 (12.63%)	**0.71**
	Feeling of warmth	2 (1.82%)	2 (2.11%)	0.91
	Black-out of vision preceding event	1 (0.91%)	1 (1.06%)	0.52
	Seizure			
	Head turning to side during the event	11 (10%)	2 (2.11%)	0.06

Demographics	Variables	Epilepsy(n = 110)	Other (n = 95)	P-Value
	Clearly described witnessed convulsion	70 (63.63%)	20 (21.05%)	**<0.001**
	Tongue biting	15 (13.64%)	4 (4.22%)	**0.001**
	Urinary incontinence	13 (13.68%)	11 (10%)	0.15
	Cyanosis observed during the event	5 (4.55%)	1 (1.06%)	0.1783
	Postictal confusion	48 (43.64%)	19 (20%)	**<0.001**

Table 3

List of 6 predictors selected by feature selection.

	LR+	LR−	# times selected
Syncope signs	1.24	0.20	10
GTC or forced head turn	3.04	0.42	10
Neuro PMH	1.70	0.61	10
Postictal confusion	1.55	0.18	10
Number of prior spells	1.17	0.52	7
Cardiac PMH	1.13	0.53	3

Table 4

Mapping from the proposed point system scores to epilepsy probability.

Scores	**≤−3**	**−2**	**−1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Predicted	0	0	0.01	0.02	0.04	0.11	0.26	0.48	0.72	0.87	0.95	0.98