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DDESVSFS: A simple, rapid and comprehensive screening tool for the Differential Diagnosis of Epileptic Seizures VS Functional Seizures

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Abstract

Objective: Functional seizures (FS) are often misclassified as epileptic seizures (ES). This study aimed to create an easy to use but comprehensive screening tool to guide further evaluation of patients presenting with this diagnostic dilemma.

Materials and methods: Demographic, clinical and diagnostic data were collected on patients admitted for video-EEG monitoring for clarification of their diagnosis. Upon discharge, patients were classified as having ES vs FS. Using the collected characteristics and video-EEG diagnosis, we created a multivariable logistic regression model to identify predictors of ES. Then, we trained an integer-coefficient model with the most frequently selected predictors, creating a pointing system coined DDESVSFS, with scores ranging from −17 to +8 points.

Results: 43 patients with FS and 165 patients with ES were recruited. In the final integer-coefficient model, 8 predictors were identified as significant in differentiating ES from FS: normal electroencephalogram (−3 points), predisposing factors for FS (−3 points), increased number of comorbidities (−3 points), semiology suggestive of FS (−4 points), increased seizure frequency (−4 points), longer disease duration (+3 points), antiepileptic polypharmacy (+2 points) and compliance with antiepileptic drugs (+3 points). Cumulative scores of ≤ −9 points carried <5% predictive value for ES, while cumulative scores of ≥ −1 points carried >95% predictive value. The model performed well (AUC: 0.923, sensitivity: 0.945, specificity: 0.698).

Conclusions: We propose DDESVSFS as a simple, rapid and comprehensive prediction score for the Differential Diagnosis of Epileptic Seizures VS Functional Seizures. Large prospective studies are needed to evaluate its utility in clinical practice.

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Keywords

Epilepsy; Seizures; Psychogenic non-epileptic seizures; Functional seizures; Screening tool; Prediction model

1. Introduction

Functional seizures (FS), previously referred to as psychogenic-non epileptic seizures (PNES),(Asadi-Pooya et al., 2020b) resemble epileptic seizures (ES), but have strong psychological rather than electrophysiological basis (Lesser, 1996). FS represent 10–30% of referrals to epilepsy specialists (Benbadis and Allen Hauser, 2000; Smith et al., 1999), and their prevalence in the general population is estimated at 2 to 33 per 100,000(Benbadis and Allen Hauser, 2000). They constitute a significant public health problem with an estimated lifetime cost per patient cohort year in the US ranging from $110–920 million (Martin et al., 1998). Quality of life (QOL) in patients with FS has been consistently shown to be worse than in patients with ES (Karakis et al., 2014b; Szaflarski et al., 2003) and the toll of the disease to the family is substantial.(Karakis et al., 2020)

FS is a heterogeneous disorder, involving complex interactions of genetic, environmental, and psychosocial factors (LaFrance and Barry, 2005). They are often hard to diagnose due to their semiological resemblance with ES(Syed et al., 2011) and the nonspecific findings commonly identified in the neurophysiological and radiological workup of these patients. (Asadi-Pooya and Homayoun, 2020; Reuber et al., 2002c). Additional reasons for this delay to diagnosis are lack of knowledge by physicians with regards to FS, negative connotation associated with their diagnosis and limited availability or access to diagnostic facilities. (Bodde et al., 2009; MacDonald et al., 2012) Misclassification can lead to unnecessary tests, treatments and social restrictions with detrimental effects for the quality of life of the individual patients and their family.(Martin et al., 1998; Reuber and Elger, 2003) Certain metrics of well-being such as occupational status may be irreversibly affected.(Walczak et al., 1995)

The gold standard for diagnosis is long term video-EEG (VEEG) monitoring.(LaFrance et al., 2013) However, it may take years for clinicians to become suspicious that the events they are confronted with are actually FS prior to referral for VEEG.(Teagarden et al., 2020) In some centers, the mean delay to diagnosis was 8.4 years,(Kerr et al., 2016) with time from symptoms onset to VEEG admission far exceeding established guidelines.(Gumnit and Walczak, 2001; Smolowitz et al., 2007) In centers where demand for VEEG exceeds capacity, patients are commonly placed on a waiting list without any of form of triage, at the cost of even more urgent referral of patients with uncontrolled epilepsy at risk for status epilepticus or sudden unexplained death. The cost of such an evaluation is substantial. (Magee et al., 2014) For all these reasons, the creation of a reliable screening tool to gauge the probability of ES vs FS and help prioritize referrals for VEEG is a clinical necessity.

There is a wealth of literature on conditionally-independent, historical features differentiating FS from ES.(Asadi-Pooya, 2017; Dickinson and Looper, 2012) A few previous attempts to create a composite prediction score are noteworthy.(Chen et al., 2019;

Kerr et al., 2018; Rao et al., 2017; Syed et al., 2009; Wardrope et al., 2020). Yet, they did not systematically examine all demographic, clinical and diagnostic parameters that have been previously identified as potentially distinguishing. Hence, the goal of the current study was to create a comprehensive but still easy-to-use screening tool that can help identify patients with greater likelihood of FS and guide accordingly more extensive evaluation.

2. Materials and methods

2.1. Participants

This investigation was approved by the institutional review board and participating patients provided informed consent. This cross-sectional study was conducted at Grady Memorial Hospital (GMH) and Emory University Hospital (EUH), two major teaching hospitals in Atlanta, Georgia, United States. Adult patients admitted electively to the Epilepsy Monitoring Unit (EMU) for continuous video-EEG (VEEG) monitoring for diagnostic purposes were asked to participate by completing a series of questionnaires with demographic and clinical information about their disease prior to their video-EEG diagnosis becoming established. Patients who were non-English speakers (i.e. those unable to independently complete the surveys in English) or unable to read and write due to mental disability were excluded. Cross-reference was performed with the electronic medical records where information on prior diagnostic work up was also gleaned. After the completion of the EMU admission, patients were classified as ES or FS based on VEEG criteria. Only patients with documented ES or FS during their stay were included in the analysis, while patients with other non-epileptic seizures (e.g. cardiac arrhythmias, sleep or movement disorders, etc.), mixed disorder (i.e. ES and FS) or unclear diagnosis were excluded. Approximately 40% of the patients with confirmed FS and 45% of those with confirmed ES returned their questionnaires. Comparing the demographics and clinical characteristics of patients with confirmed FS and ES during the EMU admission who returned their questionnaires with those who did not, no significant differences were identified.

2.2. Data collection

The following variables were collected: 1) demographic characteristics 2) clinical characteristics 3) diagnostic characteristics. Specifically, the patients provided information on the following demographic characteristics: age, gender, race, insurance, marital status, employment, education and annual household income. They also provided information of the following clinical characteristics: age of disease onset, disease duration, average number of seizures/month in the past year, self-reported injuries related to seizures, number of antiepileptic drugs (AEDs), reported compliance with AEDs, presence of predisposing factors for FS (e.g. any of the following: history of physical or sexual abuse), presence of predisposing factors for ES (e.g. any of the following: family history of ES, perinatal injury or prematurity, developmental delay, history of febrile seizure, history of prior central nervous system insult such as infection, stroke, tumor or trauma with loss of consciousness), history of substance abuse, history of injuries, number of allergies, and number of medical comorbidities (based on the past medical history/past surgical history and review of systems). Cross-reference was performed with the electronic medical records. Semiology was deemed to be suggestive of FS if one or more of the following features were provided

by the patient or witnesses of their seizures: prolonged or fragmented seizures, preserved awareness, eye closure, back arching, arrhythmic movements, no associated incontinence or tongue biting, rapid return to baseline, suggestibility, distractibility or occurrence exclusively in wakefulness. Information on prior diagnostic evaluation was gleaned from the medical records. Prior routine electroencephalogram (EEG) was dichotomized as normal if no abnormalities were detected vs abnormal if prior interictal abnormalities of any type were reported. Similarly, prior imaging [magnetic resonance imaging (MRI) in the majority of patients or computed tomography, when MRI was not available] was dichotomized as normal if no abnormalities were detected vs abnormal if abnormalities of any type were detected.

2.3. Analysis

Descriptive statistics were used for all variables. For each variable, univariate associations were performed between each characteristic and the chance of being classified as suffering from FS vs ES after completion of the EMU admission using single predictor logistic regression. Metrics reported include p-values and odds ratios (OR) with their confidence intervals (CI). To avert the risk of missing important associations when attempting to reduce type I error, we did not adjust for multiple comparisons.(Rothman, 1990).

Following similar methodology described in detail elsewhere,(Struck et al., 2017) we then created a regularized multivariable logistic regression model for ES prediction with all baseline demographic, clinical and diagnostic variables, using the least absolute shrinkage and selection operator (LASSO), also known as L1 regularization, to select a subset of predictive features. For each dependent variable, we imputed missing values group median values.

For feature selection during model fitting, we used 10-fold nested cross validation (CV). For each of the 10 rounds of 10-CV, we split the data into training (90%) and testing (10%) data. For each fold of CV, the training data was further split into training and internal validation data (90% to 10%). Models were fit for a range of L1 regularization parameter values λ, and for each value the performance was measured on the internal validation set. The global optimum value for λ was determined such that deviance is within one standard error of the value which produced the best average performance across the 10 folds. After the model was fitted on the training data, performance (AUROC, and calibration error) were assessed on the independent test set as depicted in Fig. 1A and B. We combined the features selected from each fold and selected 11 features as listed in Table 2, with corresponding model coefficients, p values, and odds ratios with 95% CI. We performed 10,000 rounds of bootstrapping to obtain 95% confidence bounds on model prediction performance statistics. Performance was quantified using area under the receiver operating curve (AUROC) and model calibration.

We further simplified the model by eliminating predictors that are less biologically relevant and less frequently selected (<5 times out of 10 CV) by the LASSO model in Table 2. We also binarized the continuous valued predictors by comparing to the group mean, i.e.., value 1 if greater than the mean value, 0 otherwise. We then trained an integer-coefficient model 2 with just 8 clinical predictors for differentiating ES from FS: normal EEG (−3 points),

predisposing factors for FS (−3 points), increased number of comorbidities (−3 points), semiology suggestive of FS (−4 points), increased seizure frequency (−4 points), longer disease duration (+3 points), antiepileptic polypharmacy (+2 points) and compliance with antiepileptic drugs (+3 points). This final simplified model is a point system, with scores ranging from −17 up to +8 points, as listed in Table 3. We again performed 10,000 rounds of bootstrapping to obtain 95% confidence bounds on model performance as depicted in Fig. 2A and B. Finally we created an standalone application in MATLAB (MathWorks, Natick, MA) to make this screening research tool readily available free of cost (see Fig. A1).

3. Results

43 patients with FS and 165 patients with ES were recruited. In the univariate analysis, there were no significant demographic differences between the two cohorts. Patients with FS had a shorter disease duration (median of 9 years with a range of 1–31 years vs 12 years with a range of 0.75–58 years, $p = 0.0001$) and higher seizure frequency compared to those with ES. The described semiology of patients with FS was strongly suggestive of their disease compared to ES (84% vs 15%, $p < 0.0001$). Patients with FS had more frequently predisposing factors for them than patients with ES (65% vs 15%, $p < 0.0001$), while both populations had predisposing factors for ES at a comparable rate. Similarly, the rates of self-reported injuries and substance abuse did not differ substantially. Patients with FS had more comorbidities and complaints in their review of systems compared to ES (12 vs nearly 7, $p < 0.0001$). Moreover, patients with FS were less commonly on antiepileptic polypharmacy (2 or more) compared to those with ES (67% vs 84%, $p = 0.02$). Their allergies count and AEDs compliance rates were comparable. The workup of patients with FS suggested more frequently a normal EEG (86% vs 38%, $p < 0.0001$) and imaging (70% vs 50%, $p = 0.02$) compared to those with ES, and when abnormalities were detected (in 33% of patients with FS on EEG and in 14% of patients with FS on imaging), these were typically nonspecific (e.g. non epileptiform abnormalities on EEG and periventricular white matter abnormalities on imaging). The results of the univariate analysis are detailed in Table 1.

In the multivariate analysis, initially 11 predictors were selected as depicted in Table 2. The performance metrics of model 1 incorporating these predictors are shown in Fig. 1A and B. The area under the receiver operative curve (AUROC) for model 1 was 0.93 (CI: 0.877–0.961), with operational point at threshold of 0.57, 0.945 sensitive and 0.698 specific. Model calibration with an error of 0.061 (CI 0.021–0.116) shows the model performed well with predicted probability of ES closely matching the true proportion of patients with ES.

As mentioned in the methodology section, we further simplified model 1 to create a point system with scores ranging from −17 up to +8 points. In the final integer-coefficient model, 8 predictors were identified as important for differentiating ES from FS: normal EEG (−3 points), predisposing factors for FS (−3 points), increased number of comorbidities (−3 points), semiology suggestive of FS (−4 points), increased seizure frequency (−4 points), longer disease duration (+3 points), antiepileptic polypharmacy (+2 points) and compliance with antiepileptic drugs (+3 points). As shown in Table 3, cumulative scores of ≤ −8 points carried <5% predictive value for ES, while cumulative scores of ≥ −1 points carried >95% predictive value. The performance metrics of the model 2 are depicted in Fig. 2A and B. The

AUROC was 0.971 (CI 0.94–0.99), with operational point at threshold of 0.65, 0.952 sensitive and 0.86 specific. In addition, the calibration error was 0.076 (CI 0.03–0.14). An illustrative example of the DDESVSFS calculator is provided in the appendix. The online version of the DDESVSFS calculator can be found in the following URL: https://cdac.massgeneral.org/tools/DDESVSFS/.

4. Discussion

This study provides evidence for 8 key factors that can help clinicians differentiate ES from FS with high accuracy. For practical purposes, we coined the DDESVSFS mnemonic (Duration of the disease, Drugs number/AEDs polypharmacy, EEG test results, Systemic complaints/Comorbidities, Volume/Frequency of seizures, Susceptibility/Predisposing factors for FS, Faithfulness/Compliance with AEDs, Semiology suggestive of FS).

4.1. Interpretation

From a demographic standpoint, the characteristics of our cohorts are in line with previous studies.(Abubakr et al., 2003) Most patients with PNES were female with a mean age of 36 years. Both FS and ES cohorts had comparable rates of social impact, as suggested by rates of employment, marriage and educational attainment, corroborating the disabling nature of both disorders.(Karakis et al., 2014a; Karakis et al., 2013, 2014b)

From a clinical standpoint, there was a delay of nearly 8 years until a diagnosis of FS is reached, highlighting the previously identified difficulty in distinguishing between FS and ES.(Reuber et al., 2002a) Reaffirming existing literature,(Karakis et al., 2014b) patients with FS had higher seizure frequency, briefer disease duration and were maintained on fewer AEDs. Predisposing factors for FS such as physical or sexual abuse were again shown to be highly prevalent.(Fiszman et al., 2004; Reuber et al., 2007) In keeping with prior studies, (Kerr et al., 2017a; Kerr et al., 2017b) patients with FS were far more likely to report comorbidities and positive symptoms in their review of systems, likely as a reflection of increased tendency towards somatization. Historical semiological features suggestive of FS were highly distinguishing.(Syed et al., 2011)

From a diagnostic standpoint, patients with FS had more frequently normal prior electrophysiologic and radiologic evaluation. When abnormalities were detected (in 14% of patients with FS on the EEG and in 30% of patients on the imaging), these were typically nonspecific (e.g. non epileptiform abnormalities on EEG and no radiological culprits of epilepsy on imaging). Similar rates have also been observed in prior work on patients with FS where 36% of patients had abnormal findings on their MRI(Asadi-Pooya and Homayoun, 2020) and 18% of patients had nonspecific abnormalities on their EEG(Reuber et al., 2002b). When we explored an alternative classification of EEG findings as normal, nonspecific and epileptiform abnormalities, and alternative classification of imaging findings as normal, nonspecific and radiological culprits of epilepsy, there was no subtantial improvement in the performance statistics of our model.

Prior attempts to create a screening tool based on clinical heuristics have been performed. Specifically, Rao et al identified the following historical features suggestive of FS: number

of declared comorbidities, history of significant psychological or physical trauma, verbal description of seizures consistent with FS, a number of declared drug allergies and number of previous medical interventions of any type.(Rao et al., 2017) In our study, we corroborated the value of the first three factors but did not identify a statistically significant difference in the number of stated allergies. Instead of a mere count of prior investigations, we focused on their actual result. In another attempt towards a predictive score, Kerr et al identified several factors associated with FS (female sex, older age of onset, mild traumatic brain injury, significant stressful events with sexual abuse) and with ES (history of febrile seizures, current employment or active student status, history of traumatic brain injury and longer delay from first seizure until VEEG).(Kerr et al., 2018) In our study, we attested to the value of significantly stressful events and shorter disease duration as predictive factors for FS but did not attain statistical significance in certain demographic (e.g. female sex, older age of onset) or clinical (e.g. predisposing factors for ES) that have been also previously reported.(Karakis et al., 2014b) Syed et al developed a self-administered 53-item FS screening questionnaire using demographics, clinical and seizure-related information, in addition to psychosocial variables. They identified high sensitivity of 85–94% and high specificity of 83–85%.(Syed et al., 2009) Contrary to our study, prior diagnostic information was not incorporated. Most recently, Chen et al utilized a witness based questionnaire(Chen et al., 2019) and Wardrobe et al utilized machine learning technology(Wardrope et al., 2020) to reach the same goal, both with promising results.

4.2. Strengths and limitations

This study attempted to develop a statistically validated screening tool using demographic, clinical and diagnostic characteristics that are readily available to a clinician evaluating a patient with events suspicious for FS vs ES in the clinic to decide on the need and urgency of VEEG monitoring. It also provided further insight into the pathophysiology of FS. We utilized a well-classified cohort of adult ES and FS patients confirmed with VEEG. The data collected were thorough and covered most of the features included in prior studies differentiating FS from ES. Cross-reference with medical records provided an additional checkpoint for accuracy.

On the other hand, there are limitations to acknowledge using self-reported patient data, such as the risk of response bias, selection bias due to attrition, recall bias and lack of generalizability to other settings (e.g. outpatient setting where the pre-test probability of functional seizures in lower than in the EMU) and cultures. Despite our best efforts to be comprehensive, it is conceivable that some important distinguishing variables between ES and FS were not investigated. The sample size of the patients with FS in our cohort was rather small and this may have prevented us from detecting additional predictors. Additionally, the population of FS with co-existing ES that constitutes an additional layer of complexity was not investigated.(Baroni et al., 2016) Last but not least, like any other predicting score, the current tool is meant to augment clinical judgement and cannot replace the need for video-EEG confirmation.

4.3. Future directions

These limitations notwithstanding, the findings of this study support the use of simple but comprehensive screening tool to differentiate FS from ES, based on historical demographic, clinical and diagnostic data. Prospective validation studies are needed to evaluate its utility in clinical practice and extend its applicability to certain FS populations not or under-represented in our study (e.g. children,(Wyllie et al., 1999) veterans,(Salinsky et al., 2011) males(Oto et al., 2005), elderly patients (Behrouz et al., 2006)) and those with co-existent ES with FS(Baroni et al., 2016), in other socioeconomic settings(Teagarden et al., 2020) and countries.(Asadi-Pooya et al., 2020a)

5. Conclusions

We propose DDESVSFS as a simple, rapid and comprehensive prediction score for the Differential Diagnosis of Epileptic Seizures VS Functional Seizures. Large prospective studies are needed to evaluate its utility in clinical practice.

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Declaration of Competing Interest

None of the authors have any declarations of interest pertinent to this study to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A

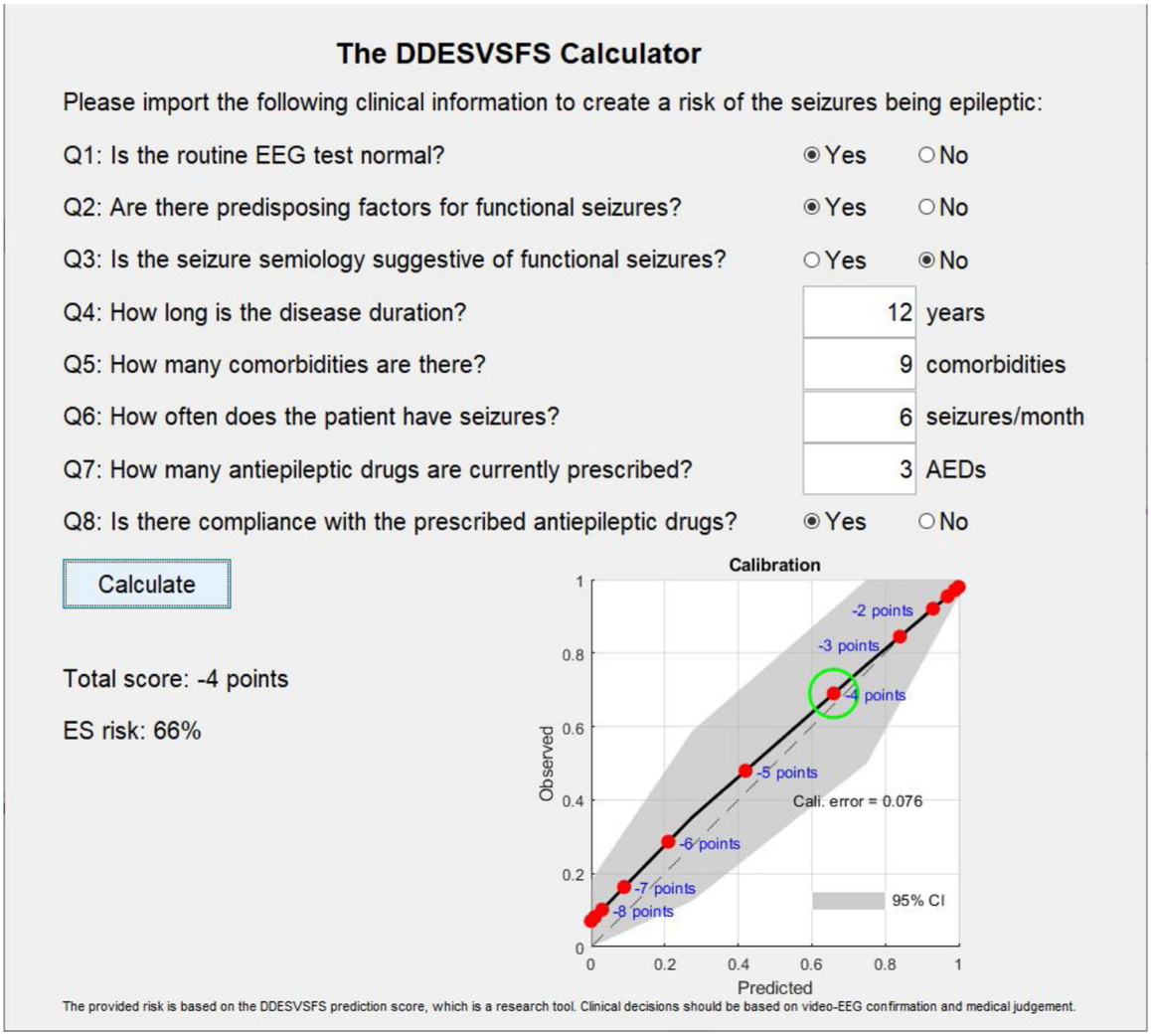

Fig. A1.
Example of the DDESVSFS calculator.

References

Abubakr A, Kablinger A, Caldito G, 2003. Psychogenic seizures: clinical features and psychological analysis. Epilepsy & behavior: E&B 4, 241–245.

Asadi-Pooya AA, 2017. Psychogenic nonepileptic seizures: a concise review. Neurol Sci 38, 935–940. [PubMed: 28275874]

Asadi-Pooya AA, Brigo F, Mesraoua B, Tarrada A, Karakis I, Hosny H, Alsaadi T, Gigineishvili D, Ali MA, Janocko NJ, Elsheikh L, Hingray C, 2020a. Clinical characteristics of functional (psychogenic nonepileptic) seizures: An international retrospective study. Epilepsy & behavior: E&B 111, 107197.

Asadi-Pooya AA, Brigo F, Mildon B, Nicholson TR, 2020b. Terminology for psychogenic nonepileptic seizures: Making the case for “functional seizures”. Epilepsy & behavior: E&B 104, 106895.

Asadi-Pooya AA, Homayoun M, 2020. Structural brain abnormalities in patients with psychogenic nonepileptic seizures. Neurol Sci 41, 555–559. [PubMed: 31713756]

Baroni G, Piccinini V, Martins WA, de Paola L, Paglioli E, Margis R, Palmini A, 2016. Variables associated with co-existing epileptic and psychogenic nonepileptic seizures: a systematic review. Seizure: the journal of the British Epilepsy Association 37, 35–40.

Behrouz R, Heriaud L, Benbadis SR, 2006. Late-onset psychogenic nonepileptic seizures. Epilepsy & behavior: E&B 8, 649–650.

Benbadis SR, Allen Hauser W, 2000. An estimate of the prevalence of psychogenic non-epileptic seizures. Seizure: the journal of the British Epilepsy Association 9, 280–281.

Bodde NM, Brooks JL, Baker GA, Boon PA, Hendriksen JG, Mulder OG, Aldenkamp AP, 2009. Psychogenic non-epileptic seizures–definition, etiology, treatment and prognostic issues: a critical review. Seizure: the journal of the British Epilepsy Association 18, 543–553.

Chen M, Jamnadas-Khoda J, Broadhurst M, Wall M, Grunewald R, Howell SJL, Koepp M, Parry SW, Sisodiya SM, Walker M, Hesdorffer D, Reuber M, 2019. Value of witness observations in the differential diagnosis of transient loss of consciousness. Neurology 92, e895–e904. [PubMed: 30804064]

Dickinson P, Looper KJ, 2012. Psychogenic nonepileptic seizures: a current overview. Epilepsia 53, 1679–1689. [PubMed: 22882112]

Fiszman A, Alves-Leon SV, Nunes RG, D'Andrea I, Figueira I, 2004. Traumatic events and posttraumatic stress disorder in patients with psychogenic nonepileptic seizures: a critical review. Epilepsy & behavior: E&B 5, 818–825.

Gumnit RJ, Walczak TS, National Association of Epilepsy, C., 2001. Guidelines for essential services, personnel, and facilities in specialized epilepsy centers in the United States. Epilepsia 42, 804–814. [PubMed: 11422341]

Karakis I, Cole AJ, Montouris GD, San Luciano M, Meador KJ, Piperidou C, 2014a. Caregiver burden in epilepsy: determinants and impact. Epilepsy Res Treat 2014, 808421. [PubMed: 24808956]

Karakis I, Montouris GD, Piperidou C, Luciano MS, Meador KJ, Cole AJ, 2013. The effect of epilepsy surgery on caregiver quality of life. Epilepsy research 107, 181–189. [PubMed: 24054427]

Karakis I, Montouris GD, Piperidou C, Luciano MS, Meador KJ, Cole AJ, 2014b. Patient and caregiver quality of life in psychogenic non-epileptic seizures compared to epileptic seizures. Seizure: the journal of the British Epilepsy Association 23, 47–54.

Karakis I, Morton ML, Janocko NJ, Groover O, Teagarden DL, Villarreal HK, Loring DW, Drane DL, 2020. Caregiver burden in psychogenic non-epileptic seizures. Seizure: the journal of the British Epilepsy Association 81, 13–17.

Kerr WT, Janio EA, Braesch CT, Le JM, Hori JM, Patel AB, Barritt SE, Gallardo NL, Bauirjan J, Chau AM, Hwang ES, Davis EC, Torres-Barba D, Cho AY, Engel J Jr., Cohen MS, Stern JM, 2017a. Diagnostic implications of review-of-systems questionnaires to differentiate epileptic seizures from psychogenic seizures. Epilepsy & behavior : E&B 69, 69–74.

Kerr WT, Janio EA, Braesch CT, Le JM, Hori JM, Patel AB, Gallardo NL, Bauirjan J, Chau AM, Hwang ES, Davis EC, Buchard A, Torres-Barba D, D'Ambrosio S, Al Banna M, Cho AY, Engel J Jr., Cohen MS, Stern JM, 2018. An objective score to identify psychogenic seizures based on age of onset and history. Epilepsy & behavior : E&B 80, 75–83.

Kerr WT, Janio EA, Braesch CT, Le JM, Hori JM, Patel AB, Gallardo NL, Bauirjan J, D'Ambrosio SR, Chau AM, Hwang ES, Davis EC, Buchard A, Torres-Barba D, Al Banna M, Barritt SE, Cho AY, Engel J Jr, Cohen MS, Stern JM, 2017b. Identifying psychogenic seizures through comorbidities and medication history. Epilepsia 58, 1852–1860. [PubMed: 28895657]

Kerr WT, Janio EA, Le JM, Hori JM, Patel AB, Gallardo NL, Bauirjan J, Chau AM, D'Ambrosio SR, Cho AY, Engel J Jr, Cohen MS, Stern JM, 2016. Diagnostic delay in psychogenic seizures and the association with anti-seizure medication trials. Seizure: the journal of the British Epilepsy Association 40, 123–126.

LaFrance WC Jr., Baker GA, Duncan R, Goldstein LH, Reuber M, 2013. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. Epilepsia 54, 2005–2018. [PubMed: 24111933]

LaFrance WC Jr., Barry JJ, 2005. Update on treatments of psychological nonepileptic seizures. Epilepsy & behavior : E&B 7, 364–374.

Lesser RP, 1996. Psychogenic seizures. Neurology 46, 1499–1507. [PubMed: 8649537]

MacDonald T, Hill A, Phan T, Fitzgerald P, Seneviratne U, 2012. Psychiatry versus general physicians: who is better at differentiating epileptic from psychogenic non-epileptic seizures? Australas Psychiatry 20, 379–383. [PubMed: 23014129]

Magee JA, Burke T, Delanty N, Pender N, Fortune GM, 2014. The economic cost of nonepileptic attack disorder in Ireland. Epilepsy & behavior : E&B 33, 45–48.

Martin RC, Gilliam FG, Kilgore M, Faught E, Kuzniecky R, 1998. Improved health care resource utilization following video-EEG-confirmed diagnosis of nonepileptic psychogenic seizures. Seizure : the journal of the British Epilepsy Association 7, 385–390.

Oto M, Conway P, McGonigal A, Russell AJ, Duncan R, 2005. Gender differences in psychogenic non-epileptic seizures. Seizure : the journal of the British Epilepsy Association 14, 33–39.

Rao SR, Slater JD, Kalamangalam GP, 2017. A simple clinical score for prediction of nonepileptic seizures. Epilepsy & behavior : E&B 77, 50–52.

Reuber M, Elger CE, 2003. Psychogenic nonepileptic seizures: review and update. Epilepsy & behavior : E&B 4, 205–216.

Reuber M, Fernandez G, Bauer J, Helmstaedter C, Elger CE, 2002a. Diagnostic delay in psychogenic nonepileptic seizures. Neurology 58, 493–495. [PubMed: 11839862]

Reuber M, Fernandez G, Bauer J, Singh DD, Elger CE, 2002b. Interictal EEG abnormalities in patients with psychogenic nonepileptic seizures. Epilepsia 43, 1013–1020. [PubMed: 12199726]

Reuber M, Fernandez G, Helmstaedter C, Qurishi A, Elger CE, 2002c. Evidence of brain abnormality in patients with psychogenic nonepileptic seizures. Epilepsy & behavior : E&B 3, 249–254.

Reuber M, Howlett S, Khan A, Grunewald RA, 2007. Non-epileptic seizures and other functional neurological symptoms: predisposing, precipitating, and perpetuating factors. Psychosomatics 48, 230–238. [PubMed: 17478592]

Rothman KJ, 1990. No adjustments are needed for multiple comparisons. Epidemiology 1, 43–46. [PubMed: 2081237]

Salinsky M, Spencer D, Boudreau E, Ferguson F, 2011. Psychogenic nonepileptic seizures in US veterans. Neurology 77, 945–950. [PubMed: 21893668]

Smith D, Defalla BA, Chadwick DW, 1999. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. QJM : monthly journal of the Association of Physicians 92, 15–23.

Smolowitz JL, Hopkins SC, Perrine T, Eck KE, Hirsch LJ, O'Neil Mundinger M, 2007. Diagnostic utility of an epilepsy monitoring unit. Am J Med Qual 22, 117–122. [PubMed: 17395968]

Struck AF, Ustun B, Ruiz AR, Lee JW, LaRoche SM, Hirsch LJ, Gilmore EJ, Vlachy J, Haider HA, Rudin C, Westover MB, 2017. Association of an Electroencephalography-Based Risk Score With Seizure Probability in Hospitalized Patients. JAMA Neurol 74, 1419–1424. [PubMed: 29052706]

Syed TU, Arozullah AM, Loparo KL, Jamasebi R, Suciu GP, Griffin C, Mani R, Syed I, Loddenkemper T, Alexopoulos AV, 2009. A self-administered screening instrument for psychogenic nonepileptic seizures. Neurology 72, 1646–1652. [PubMed: 19433737]

Syed TU, LaFrance WC Jr., Kahriman ES, Hasan SN, Rajasekaran V, Gulati D, Borad S, Shahid A, Fernandez-Baca G, Garcia N, Pawlowski M, Loddenkemper T, Amina S, Koubeissi MZ, 2011. Can semiology predict psychogenic nonepileptic seizures? A prospective study. Annals of neurology 69, 997–1004. [PubMed: 21437930]

Szaflarski JP, Hughes C, Szaflarski M, Ficker DM, Cahill WT, Li M, Privitera MD, 2003. Quality of life in psychogenic nonepileptic seizures. Epilepsia 44, 236–242. [PubMed: 12558580]

Teagarden DL, Morton ML, Janocko NJ, Groover O, Villarreal HK, Evans L, Drane DL, Karakis I, 2020. Socioeconomic disparities in patients with psychogenic nonepileptic seizures and their caregivers. Epilepsy & behavior : E&B 107160.

Walczak TS, Papacostas S, Williams DT, Scheuer ML, Lebowitz N, Notarfrancesco A, 1995. Outcome after diagnosis of psychogenic nonepileptic seizures. Epilepsia 36, 1131–1137. [PubMed: 7588458]

Wardrope A, Jamnadas-Khoda J, Broadhurst M, Grunewald RA, Heaton TJ, Howell SJ, Koepp M, Parry SW, Sisodiya S, Walker MC, Reuber M, 2020. Machine learning as a diagnostic decision aid

for patients with transient loss of consciousness. Neurol Clin Pract 10, 96–105. [PubMed: 32309027]

Wyllie E, Glazer JP, Benbadis S, Kotagal P, Wolgamuth B, 1999. Psychiatric features of children and adolescents with pseudoseizures. Archives of pediatrics & adolescent medicine 153, 244–248. [PubMed: 10086400]

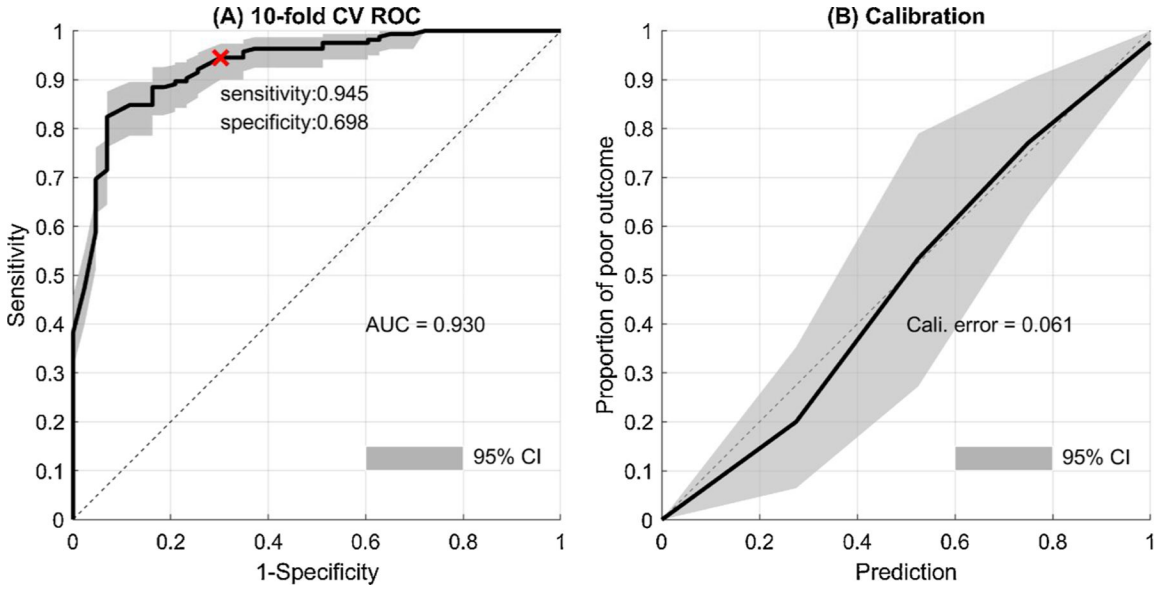

Fig. 1.

A and B: Performance metrics of prediction model 1 with (A) the ROC curve and (B) the model calibration.

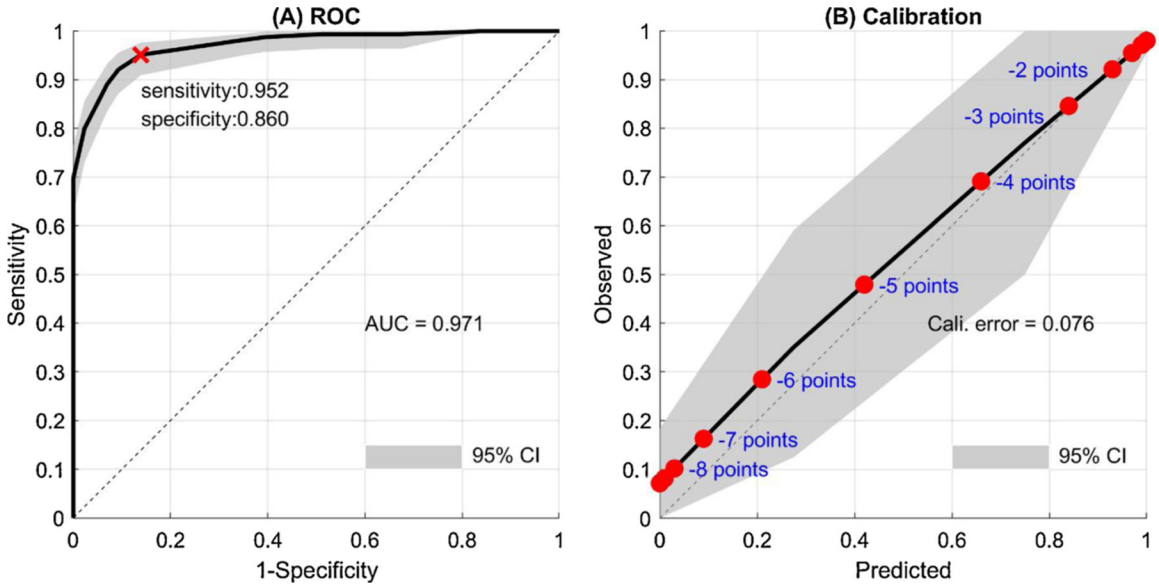

Fig. 2.

A and B: Performance metrics of prediction model 2 with (A) the ROC curve and (B) calibration with the predicted DDESVEFS scores.

Table 1

Demographic, clinical and diagnostic characteristics of patients with FS and ES.

	FS (N = 43)	ES (N = 165)	OR	95% CI	P value
Demographic characteristics					
Age (Mean, SD)	36.40 (12.69)	36.85 (12.46)	-	-	0.83*
Gender: Female (n, %)	33 (77%)	103 (62%)	0.50	0.23–1.09	0.08#
Race: Caucasian (n, %)	22 (51%)	104 (63%)	1.62	0.82–3.20	0.15#
Insurance: Private (n, %)	29 (67%)	100 (61%)	0.74	0.36–1.51	0.41#
Marital status: Married (n, %)	13 (30%)	54 (33%)	1.06	0.54–2.32	0.75#
Employment: No (n, %)	28 (65%)	108 (65%)	1.01	0.50–2.05	0.96#
Education: Some college or more (n, %)	30 (70%)	109 (66%)	0.84	0.40–1.74	0.64#
Income (Median, IQR)	$45,000 (23,750)	$45,000 (47,000)	-	-	0.89&
Clinical characteristics					
Predisposing factors for ES: Yes (n, %)	28 (65%)	113 (68%)	1.16	0.57–2.36	0.67#
Predisposing factors for FS: Yes (n, %)	28 (65%)	24 (15%)	0.09	0.04–0.19	<0.0001#
Substance abuse: Yes (n, %)	8 (19%)	31 (19%)	1.01	0.42–2.39	0.97#
FS suggestive semiology by history: Yes (n, %)	36 (84%)	24 (15%)	0.03	0.01–0.08	<0.0001#
Injuries: Yes (n, %)	32 (74%)	125 (76%)	1.07	0.49–2.32	0.85#
Number of ≥2 AEDs: Yes (n, %)	29 (67%)	138 (84%)	2.46	1.15–5.27	0.02#
Compliance with AEDs: Yes	33 (77%)	137 (83%)	1.48	0.65–3.35	0.34#
Allergies (Mean, SD)	1.28 (1.76)	1.15 (1.68)	-	-	0.64*
Comorbidities (Mean, SD)	12.00 (7.55)	6.68 (3.70)	-	-	<0.0001*
Seizure frequency (seizures/month) (Median, IQR)	3 (18.75)	3 (4)	-	-	0.001&
Age of disease onset (years) (Mean, SD)	23.95 (13.07)	20.64 (13.20)	-	-	0.14*
Disease duration (years) (Median, IQR)	9 (10.75)	12 (15.25)	-	-	0.0001&
Diagnostic characteristics					
EEG: Normal (n, %)	37 (86%)	63 (38%)	0.10	0.04–0.25	<0.0001#
Imaging: Normal (n, %)	30 (70%)	83 (50%)	0.44	0.21–0.90	0.025#

FS: Functional Seizures, ES: Epileptic Seizures, OR: Odds Ratio, CI: Confidence Intervals, SD: Standard Deviation, IQR: Interquartile Range, AEDs: Antiepileptic Drugs, EEG: Electroencephalogram

Fischer exact test.

* Student t-test.

& Wilcoxon Rank Sum Test.

Table 2

List of 11 predictors selected by LASSO with multi-variate statistics.

Predictor	Number of times selected	P value	Odds Ratio	95% Confidence Intervals
Race	2	0.086	0.263	0.057–1.209
Predisposing factors for FS	10	0.001	0.097	0.024–0.390
FS suggestive semiology	10	<0.0001	0.034	0.007–0.162
Injuries	4	0.048	5.684	1.017–31.77
Number of AEDs	8	0.096	4.232	0.774–23.13
Compliance with AEDs	8	0.065	5.217	0.905–30.08
Comorbidities	10	0.002	0.778	0.677–0.915
Seizure frequency	10	<0.0001	0.945	0.915–0.975
Disease duration	10	0.038	1.093	1.005–1.189
Normal EEG	10	0.012	0.090	0.014–0.592
Normal imaging	1	0.974	0.976	0.226–4.207

LASSO: least absolute shrinkage and selection operator, FS: Functional seizures, AEDs: Antiepileptic Drugs, EEG: Electroencephalogram.

Table 3

Mapping from the proposed pointing system scores to predictive value of ES.

Scores	**≤−8**	**−7**	**−6**	**−5**	**−4**	**−3**	**−2**	**≥−1**
ES Predictive Value	<5%	9%	21%	42%	66%	84%	93%	95%

ES: Epileptic seizures.