Predictive models in the diagnosis and treatment of autoimmune epilepsy


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SUMMARY

Objective: To validate predictive models for neural antibody positivity and immunotherapy response in epilepsy.

Methods: We conducted a retrospective study of epilepsy cases at Mayo Clinic (Rochester-MN; Scottsdale-AZ, and Jacksonville-FL) in whom autoimmune encephalopathy/epilepsy/dementia autoantibody testing profiles were requested (06/30/2014-06/30/2016). An Antibody Prevalence in Epilepsy (APE) score, based on clinical characteristics, was assigned to each patient. Among patients who received immunotherapy, a Response to Immunotherapy in Epilepsy (RITE) score was assigned. Favorable seizure outcome was defined as >50% reduction of seizure frequency at the first follow-up.

Results: Serum and cerebrospinal fluid (CSF) from 1,736 patients were sent to the Mayo Clinic Neuroimmunology Laboratory for neural autoantibody evaluation. Three hundred eighty-seven of these patients met the diagnostic criteria for epilepsy. Central nervous system (CNS)–specific antibodies were detected in 44 patients. Certain clinical features such as new-onset epilepsy, autonomic dysfunction, viral prodrome, faciobrachial dystonic seizures/oral dyskinesia, inflammatory CSF profile, and mesial temporal magnetic resonance imaging (MRI) abnormalities had a significant association with positive antibody results. A significantly higher proportion of antibody-positive patients had an APE score ≥4 (97.7% vs. 21.6%, p < 0.01). Sensitivity and specificity of an APE score ≥4 to predict presence of specific neural auto-antibody were 97.7% and 77.9%, respectively. In the subset of patients who received immunotherapy (77), autonomic dysfunction, faciobrachial dystonic seizures/oral dyskinesia, early initiation of immunotherapy, and presence of antibodies targeting plasma membrane proteins (cell-surface antigens) were associated with favorable seizure outcome. Sensitivity and specificity of a RITE score ≥7 to predict favorable seizure outcome were 87.5% and 83.8%, respectively.

Significance: APE and RITE scores can aid diagnosis, treatment, and prognostication of autoimmune epilepsy.

KEY WORDS: Epilepsy, Immunotherapy, Autoimmune limbic encephalitis, Paraneoplastic limbic encephalitis, Diagnosis, Predictive model.
A significant proportion of cryptogenic epilepsies has been attributed to autoimmunity, or a possible autoimmune cause (15–20%). Establishing an autoimmune etiology has a large impact on management (immunotherapeutic in addition to standard anticonvulsants), and influences seizure outcomes. A recent, prospective study reported serologic findings among consecutively evaluated patients presenting with epilepsy of unknown etiology. Twenty percent of cases were neural antibody (Ab) seropositive, indicative of a possible autoimmune cause. The same study also evaluated a scoring system known as the Antibody Prevalence in Epilepsy (APE) score, as a model to predict the detection of these Abs based on patients’ clinical presentation and initial neurologic evaluation. The score was prospectively assigned to all enrolled patients prior to Ab testing. An APE score of ≥4 has a sensitivity and specificity of 82.6% and 82.0%, respectively. After excluding voltage gated potassium channel-complex (VGKCc) Ab seropositive cases with negative leucine-rich glioma-inactivated 1 (LGI-1) Ab results, the sensitivity of the APE score increased to 100% (specificity, 79.4%).

A scoring system based on clinical features and initial neurologic assessment of patients with epilepsy may enable earlier clinical diagnosis while specific neural Ab results are awaited. Prediction of positive immunotherapeutic response justifies prompt initiation of immunotherapy potentially limiting the extent of neurologic disability. In addition, a validated scoring system with high sensitivity would obviate the need for extensive autoimmune serologic testing and may help direct resources in evaluating alternative etiologies.

In this study, we validate the APE score as a predictive model of neural Ab positivity in all epilepsy cases, in addition to cryptogenic cases. Patients were ascertained from Mayo Clinic’s index-linked medical record system by searching for those whose serum, cerebrospinal fluid (CSF), or both, were evaluated in the Neuroimmunology Laboratory. We modified the score to assess the response to immunotherapy and outcome, and thus validate a second outcome measure, the Response to Immunotherapy in Epilepsy (RITE) score.

**Methods**

The Mayo Clinic Institutional Review Board (IRB) approved the study (IRB number 08-006647).

We conducted a retrospective chart review using electronic medical records of three Mayo Clinic centers (Rochester, MN; Scottsdale, AZ; and Jacksonville, FL), Figure 1. Clinical data were collected from patients (adults and children) in whom autoimmune encephalopathy, autoimmune epilepsy, or autoimmune dementia evaluations of serum, CSF, or both, were requested and performed in the Neuroimmunology Laboratory (June 30, 2014 to June 30, 2016). Patient inclusion was further refined using the Advanced Cohort Explorer Data Retrieval tool to ascertain those cases with diagnoses of epilepsy or recurrent seizures (International Classification of Diseases [ICD] 9 345, ICD 10G40). All records with epilepsy or seizure diagnoses were reviewed to confirm epilepsy diagnoses: the presence of two unprovoked seizures at least 24 h apart or one unprovoked seizure with additional clinical features suggesting a high probability of recurrence. Demographic and clinical data including epilepsy etiology, Ab type, APE score variables, and duration of symptom onset to treatment were collected (Table 1A). Among patients who received immunotherapy, RITE scores were calculated for each patient (Table 1B). The RITE score included variables from the APE score and two additional items. These were factors previously demonstrated to influence response to immune therapies in autoimmune epilepsy: (1) early initiation of immunotherapy (within 6 mo of diagnosis), (2) detection of an Ab reactive with the extracellular domain of a neural plasma membrane protein (cell-surface antigen), which would indicate likely Ab pathogenicity.

All serum and CSF specimens were evaluated by: (1) standardized indirect immunofluorescence assays (IFAs) for immunoglobulin G (IgG) Abs with the following specificities: anti-neuronal nuclear antibody (ANNA)-1 [anti-Hu], ANNA-2 [anti-Ri], ANNA-3, amphiphysin; Purkinje-cell cytoplasmic (PCA-1) [anti Yo], PCA-2, and PCA-Tr [DNER]; collapsin response-mediator protein (CRMP)-5, anti-glial/neuronal nuclear (AGNA)-1; glial fibrillary acidic protein (GFAP); N-methyl-d-aspartate (NMDA) receptor [GluN1 subunit], z-aminos-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor [GluA1 and GluA2 subunits], dipeptidyl-peptidase-like protein 6 (DPPX), metabotropic glutamate receptor (mGluR) 1, 7-aminobutyric acid (GABA) B receptor, and GABA A receptor; and (2) radioimmunoprecipitation assays (RIAs) for Abs...
targeting neuronal VGKCc, muscle (α1) nicotinic acetylcholine receptor, and neuronal ganglionic (α3) acetylcholine receptor, P/Q type voltage-gated calcium channel (VGCC), N-type VGCC and glutamic acid decarboxylase, 65 isoform (GAD65), (3) enzyme-linked immunosorbent assay for striational Abs, (4) cell-based assays (CBAs) using human embryonic kidney 293 cells transfected with appropriate expression plasmids to detect Abs targeting NMDA receptor, AMPA receptor, and GABAB receptors (Euromimmun, Lubeck, Germany). For all VGKCc IgG-positive specimens, CBAs for LGI-1 and contactin-associated protein 2 (CASPR2) IgG using transfected human embryonic kidney 293 cells were performed (Euroimmun, Lubeck, Germany). Those yielding IFA patterns consistent with GFAP Ab, DPPX, mGluR1, and mGluR5 were confirmed by CBAs on transfected cell lines on a research basis (in-house developed or Euroimmun).12–16

Fifteen patients with VGKCc Ab detected by RIA but negative by LGI-1 and CASPR2 Ab testing (low specificity for neurologic autoimmunity) were excluded from the central nervous system (CNS)–specific Ab-positive group for further analysis.17–19 In addition, only patients with GAD65
Ab values with neurologic specificity (≥ 20 nmol/L), 12 of 31 cases, were included in the analyses.20

Univariate analyses of nominal and interval variables were performed using chi-square and Mann-Whitney U-tests, respectively. A multivariate regression model was utilized to compare variables significant by univariate analyses. Receiver-operating curve (ROC) analyses were used to evaluate the predictive scoring models.

Results

Serum, CSF, or both, from 1,736 patients referred for autoimmune encephalopathy, dementia, or epilepsy antibody evaluations were tested in the Mayo Clinic Neuroimmunology Laboratory between June 30, 2014 to June 30, 2016. Three hundred eighty-seven of those patients had a diagnosis of epilepsy.11 Only serum was submitted for 321 patients, only CSF for 20 patients, and for 46 patients both specimen types were submitted. Two hundred seventy-nine patients had adult-onset epilepsy (median 49 years, range 18–89 years) and 108 cases had childhood-onset epilepsy (median 4 years, range 0.5–17). Among 387 patients with epilepsy, 97 patients were positive for one or more neural autoantibodies (25%). Forty-four patients had an autoimmune CNS-specific Ab profile, after 53 patients with the following antibody specificities were excluded: low titer...
GAD-65 (<20 nmol/L), VGKCc, where LGI1 and CASPR2 Ab testing was negative, acetylcholine receptor (muscle or neuronal), striational, and VGCC (P/Q- and N-type).

Among 44 cases, 34 were adults and 10 were children. Serum VGKCc Ab (median 0.31 nmol/L; range 0.15–1.28 nmol/L) with coexisting LGI-1 Ab was the most common finding (N = 17, 38.6%), followed by high-titer serum GAD65 Ab (N = 12, median 300 nmol/L; range 107–1,936 nmol/L), NMDA-R Ab (N = 6, range 1:16–1:512 [all CSF], CBA positive), ANNA-1 Ab (N = 2, 1:256 [CSF], and 1:7,860 [serum]), AMPA-R Ab (N = 2, 1:1,920, and 1:7,860 [both serum], CBA positive), GFAPs Ab (N = 2, 1:16 and 1:64 [both CSF], CBA positive), serum VGKCc Ab (0.10 nmol/L) with coexisting CASPR2 antibody (N = 1), CRMP-5 Ab (N = 1, titer 1:512 [CSF]), and ANNA-2 (N = 1, 1:7,860 [serum]).

Clinical features found more commonly among 44 CNS-specific Ab-positive patients compared to the other 343 patients included (Table 2): cognitive dysfunction (81.6% vs. 38.6%, p < 0.01), new-onset epilepsy (seizure onset within 1 year of antibody evaluation, 72.1% vs. 33.1%, p < 0.01), neuropsychiatric dysfunction (72.7% vs. 25.7%, p < 0.001), viral prodrome (20.5% vs. 2.6%, p < 0.01), faciobrachial dystonic seizures (FBDS) or facial dyskinesias (29.5% vs. 0.6%, p < 0.01), autonomic instability (18.2% vs. 1.5%, p < 0.01), new-onset epilepsy (seizure onset ≤10 mm Hg fall in systolic pressure or ≥10 mm Hg fall in diastolic pressure within 3 min of standing), hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, or cardiac asystole, rhinorrhea, sore throat, low-grade fever, localization of seizure determined based on ictal or interictal findings on electroencephalography (EEG), agitation, aggressiveness, emotional lability.

A significantly higher proportion of the CNS-specific Ab-positive patients had APE score ≥4 (97.7% vs. 21.6%, p < 0.01), Figure 1. Median APE scores were also significantly higher among antibody-positive patients (median 6 [range 3–12] vs. median 2 [range 0–9], p < 0.01). Based on ROC analysis with a cutoff ≥4, the sensitivity and specificity of the APE score to predict presence of CNS-specific auto-Ab were 97.7% and 77.9%, with area under the curve (AUC) of 0.93 (Fig. S1A). On analysis of test performance in only cases of epilepsy of unknown etiology (262), the results were similar (sensitivity 97.7%, specificity 78.9%, and AUC of 0.94), Figure S1B.
In the subset of patients who received immunotherapy (N = 77), factors associated with favorable seizure outcome included (Table 3): neural Ab positivity (72.5% vs. 27%, p < 0.01), plasma membrane protein Ab positivity (57.5% vs. 2.7%, p < 0.01), new-onset epilepsy (90.0% vs. 27%, p < 0.01), autonomic dysfunction (20% vs. 0%, p < 0.05), FBDS or oral dyskinesias (35% vs. 5.4%, p < 0.01), and initiation of immunotherapy within 6 months of symptom onset (82.5% vs. 16.2%, p < 0.01). A significantly higher proportion of patients with an APE score ≥4 (92.5% vs. 54.1%, p < 0.01) responded to immunotherapy with 50% reduction in seizure frequency on first follow-up visit after completion of immunotherapy trial. The APE score had a high sensitivity (90%) in predicting response to initial immunotherapy, but low specificity (43.4%), Figure S2A. The interval between immunotherapy initiation and follow-up did not differ significantly between responders (median 81 days, 35 to 320 days) and nonresponders (median 92 days, 28 to 425 days).

Early initiation of therapy (<6 months from symptom onset) and detection of a plasma membrane protein Ab (NMDA-R, LGI-1, CASPR2, AMPA-R, GABA	extsubscript{B}-R Abs) but not neuronal nuclear or cytoplasmic Abs (GAD65 [titer>20 nmol/L], ANNA-1, ANNA-2, CRMP-5, and GFAP Abs) were independent predictors of favorable seizure outcome (p < 0.01). ROC analysis of the RITE score determined an AUC of 0.89, Fig. S2B. The sensitivity and specificity values of RITE score ≥7 were 87.5% and 83.8%, respectively.

Patients who responded to immunotherapy (n = 5), despite having a RITE score <7 (Fig. 2), included one patient with GAD65 Ab (115 nmol/L [serum]), one patient with Parry-Romberg syndrome, one with VGKCc Ab (0.18 nmol/L [serum], LGI-1, and CASPR-2 Ab negative), and two patients with multiple enhancing lesions on MRI of brain suggesting an autoimmune etiology or vasculitis but no neural autoantibody detected in serum or CSF (brain biopsy showed nonspecific gliosis). Among six patients with RITE score ≥7 but unfavorable seizure outcome, two patients had high titer GAD-65 Ab (300 nmol/L and 1236 nmol/L [both serum]), one patient had LGI-1 Ab with delayed immunotherapy initiation (>2 years after symptom onset), one patient had mesial temporal sclerosis, one patient had suspected paraneoplastic limbic encephalitis (underlying breast cancer) but no neural-specific antibodies detected in serum or CSF, and one patient had CNS vasculitis.

**Discussion**

In this retrospective study, we have validated the utility of APE and RITE scores as predictive models for...
autoimmune epilepsy and initial immunotherapy response, respectively. With a sensitivity of 97.7%, the APE score has the potential to serve as a useful tool for identifying patients in whom contemporary neural autoantibody profiles may be negative. Following the diagnostic evaluation, the RITE score may help select patients for immunotherapy trials, and aid in counseling patients regarding the likelihood of improving after treatment.

The APE score is a composite of multiple factors that, in aggregate, indicate the likelihood of an autoimmune etiology. Each variable individually is neither specific nor sensitive for an autoimmune diagnosis, but as a composite score has now been validated in two independent cohorts (UT Southwestern [prospectively]² and Mayo Clinic [retrospectively]) as a predictive model, which could easily be implemented clinically.

We extended assignment of APE score to patients in whom an alternative (genetic/structural/metabolic) was suspected, along with those with epilepsy of unknown etiology.² We also broadened the scope of the study to include children. This is of importance for validation of a scoring system, which might be applied on initial clinical evaluation of the patients. With continued surveillance, many patients who were initially suspected to have a cryptogenic cause may be found to have an alternative etiology. Antibodies such as GFAPα, DPPX, mGluR1, mGluR5, and CASPR-2, which were not evaluated in the previously published study evaluating APE score, were tested on sera and/or CSF samples. In addition, LGI-1 and CASPR-2 Ab-negative VGKCc Ab-seropositive cases, which were included as cases previously,² were not included in this current analyzed cohort because recent studies have demonstrated low specificity of this antibody profile for neurologic autoimmunity.¹⁸,¹⁹

The likelihood of immunotherapy response is a critical concern for patients and physicians alike in cases of intractable epilepsy with suspected autoimmune etiology.⁴ At times, decisions to initiate immunotherapy can be complicated, especially if neural Ab results are either negative or nonspecific (e.g., low titer GAD-65, VGKCc Ab positive, but LGI-1 and CASPR-2 Ab negative). In such circumstances the RITE score provides an evidence-based approach to guide therapeutic decision making. With a sensitivity of 87.5%, the RITE score should be informative when counseling patients regarding likelihood of immune therapy response. In addition, among cases of intractable epilepsy with unknown etiology, early identification of patients with poor immunotherapy responses are critical for

Figure 2.
Distribution of patients initiated on immunotherapy regimen in either the inpatient or outpatient setting based on their seizure outcome—responders (>50% reduction in seizure frequency) and nonresponders. Responders and nonresponders are further divided into subgroups based on their RITE score followed by depiction of choice of initial immunotherapy agent. IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; PLEX, plasmapheresis. ⁵5-day course of IVMP: 1 g, i.v., once per day for 5 consecutive days. ⁵5-day course of IVIG: 0.4 g/kg, i.v., once per day for 5 consecutive days. ⑤5 sessions of PLEX, every alternate day. *Enrolled into 12-week IVMP trial: 1 g, i.v., once per day for 3 consecutive days, then once weekly for 5 weeks, followed by once every 2 weeks for 6 weeks, for a total of 12 weeks of therapy. ⁶Enrolled into 12-week IVIG trial: 0.4 g/kg daily for 3 days followed by 0.4 g/kg every week for 6 weeks and then every 2 weeks for 6 weeks.

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selecting potential candidates to receive alternative therapeutic approaches such as epilepsy surgery. This modality may be beneficial in certain nonimmune therapy-responsive individuals with autoimmune epilepsy and unifocal seizure localization.\(^{21,22}\) Low scores in certain patients might also support redirection of diagnostic resources away from autoimmunity, and toward other etiologies. It is important to emphasize how these scores can facilitate early diagnosis, as the present data demonstrated that responder rate correlates with earlier treatment.

The two scores may also work together in other ways. For example, if the APE score is high (\(\geq 4\)), or a patient is found to have a neural Ab with high predictive value for an autoimmune cause but the RITE score predicts poor response to initial immunotherapy, earlier use of second-line agents (such as rituximab and cyclophosphamide) may need to be considered.\(^{23}\)

The majority of autoimmune diseases including autoimmune epilepsies are chronic conditions. Management of these conditions can be exceedingly expensive. According to the National Institute of Allergy and Immunology, annual autoimmune disease treatment costs have been estimated to be greater than $100 billion in the United States.\(^{24,25}\) Due to lack of randomized control trials for management of certain autoimmune conditions, such as limbic encephalitis or autoimmune epilepsy, and lack of approval of immunotherapy by agencies such as the U.S. Food and Drug Administration (FDA), many insurance companies refuse to reimburse costs.\(^{26}\) This may lead to delay in treatment or no treatment, thereby leading to lifelong neurologic deficits. A scoring system that predicts likelihood of response to immunotherapy could serve as an evidence-based means to reassure health insurers of the nonexperimental nature of treatment recommendations.

Response of intractable epilepsy to immunotherapy is supportive of an autoimmune cause but it cannot be considered, in isolation, as confirmatory.\(^{5}\) Many patients with immune-mediated conditions may remain refractory despite standard immunotherapy, especially paraneoplastic limbic encephalitis cases with Abs reactive with intracellular antigens (e.g. Ma1 and Ma2, ANNA-1, or CRMP-5 Abs) or patients in whom there is a significant delay in immunotherapy initiation.\(^{5,27}\) Conversely, conditions such as infantile spasms or electrical status epilepticus of sleep and Landau-Kleffner syndrome, which have not been proven to have a primary immune-mediated etiology, may respond favorably to corticosteroids.\(^{28,29}\) Furthermore, some other disorders, such as Rasmussen’s encephalitis and Parry-Romberg syndrome, appear to be immune-mediated, but responses to immunotherapy are variable.\(^{30,31}\) Therefore, the use of the RITE score should be limited to encouraging initiation of an immunotherapy trial, rather than confirming an autoimmune diagnosis.

Limitations of our approach included the repertoire of Abs tested, which did not include certain Abs (such as glycinereceptor Ab or Ma1/Ma2 Ab) in all patients. Some patients with autoimmune epilepsies lack any currently identifiable Ab biomarker\(^{32}\); therefore, sensitivity and specificity values for APE and RITE scores obtained in this study may be revised in the future with recognition of new neural antibodies. In addition, the low referral rate of paired serum and CSF specimens may have affected sensitivity. Retrospective design of this study is a limitation and confounders such as change in antiseizure medications, especially in nonresponders or critically ill patients in the inpatient setting, could not be controlled for.

Various guidelines have been suggested for identifying cases with potential autoimmune etiology, but none of them are as objective as a scoring system.\(^{4,17,33,34}\) In addition, none of them have specifically targeted patients with epilepsy or have been validated in clinical settings prospectively or retrospectively. For the most part, they are based on expert opinion rather than evaluated for their sensitivity or specificity using an outcome variable such as Ab positivity or immunotherapy response.\(^{4,34}\) In this regard APE and RITE scores provide a novel evidence-based approach in diagnosing and managing autoimmune epilepsy. They also could serve as models for development of similar predictive scoring systems for other autoimmune neurologic conditions such as ataxias, dementia, and neuropathy.

**DISCLOSURE OF CONFLICTS OF INTEREST**

Divyanshu Dubey: None. Jaysingh Singh: None. Jeffrey W. Britton: Dr. Britton is a co-investigator intravenous immunoglobulin in LGI-1 encephalitis clinical trial. Sean J. Pittock: Dr. Pittock and Mayo Clinic have a financial interest in patents (12/678,350 filed 2010 and #12/573,942 filed 2008) that relate to functional AQP4/neuromyelitis optica (NMO)-IgG assays and NMO-IgG as a cancer marker; Dr. Pittock has provided consultation to Alexion Pharmaceuticals, Medimmune, and Chugai Pharma U.S.A. but has received no personal fees or personal compensation for these consulting activities. All compensation for consulting activities is paid directly to Mayo Clinic. Dr. Pittock has received a research grant from Alexion pharmaceuticals for an investigator-initiated study as well as support from the National Institutes of Health (NIH; RO1 NS065829-01) and the Guthy Jackson Charitable Foundation for NMO research. Eoin P. Flanagan: None. Vanda A. Lennon: Dr. Lennon receives royalties from RSR/Kronus for sale of aquaporin-4 autoantibody testing kits and for commercial aquaporin-4 autoantibody testing performed outside Mayo Clinic; received research support from NIH; and has a financial interest in the following intellectual property: “Marker for Neuromyelitis Optica.” A patent has been issued for this technology, and it has been licensed to commercial entities. She has received cumulative royalties of greater than the federal threshold for significant financial interest from the licensing of these technologies, but receives no royalties from the sale of these tests by Mayo Medical Laboratories; however, Mayo Collaborative Services, Inc., does receive revenue for conducting these tests. Jan-Mendelt Tillema: None. Elaine Wirrell: None. Cheolsoo Shin: None. Elison So: None. Gregory D. Cascino: None. Dean M. Wingerchuk: None. Matthew T. Hoerth: None. Jerry J Shih: Dr. Shih is on the Speakers’ Bureau for Eisai. Katherine C. Nickels: None. Andrew McKeon: Dr. McKeon has received research support from Medimmune and Euroimmun. 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.
REFERENCES


Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 (A, B) Receiver operating characteristic (ROC) curve demonstrating performance of APE score as binary classifier system (APE score ≥ 4) in predicting positive serum and/or CSF Abs in all epilepsy cases (1A) and among patients with epilepsy of unknown etiology (1B). Using a cutoff of ≥4 leads to maximum sensitivity and specificity of 97.7% and 77.9%, respectively, among all epilepsy cases and 97.7% and 78.9%, respectively, among epilepsies of unknown etiology. Area under the curve (probability that the binary classifier system will a rank randomly chosen positive instance higher than a randomly chosen negative instance) for APE score ≥4 among all epilepsy cases was 0.93 for all epilepsy cases and 0.94 for epilepsy of unknown etiology.

Figure S2 (A, B) Receiver operating characteristic (ROC) curve demonstrating performance of APE score (A) and RITE score (B) in predicting positive seizure outcomes among patients with epilepsy who received immunotherapy. Using a cutoff of ≥4 for APE score leads to maximum sensitivity and specificity of 92.5% and 44.6%, respectively, and cutoff at ≥7 for RITE score leads to maximum sensitivity and specificity of 87.5% and 83.8%, respectively. Area under the curve for APE score ≥4 was 0.79 and RITE score ≥7 was 0.89.