OBSERVATIONAL STUDY

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Association of Epileptiform Activity With Outcomes in Toxic-Metabolic Encephalopathy

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IMPORTANCE: The clinical significance of epileptiform abnormalities (EAs) specific to toxic-metabolic encephalopathy (TME) is unknown.

OBJECTIVES: To quantify EA burden in patients with TME and its association with neurologic outcomes.

DESIGN, SETTING, AND PARTICIPANT: This is a retrospective study. A cohort of patients with TME and EA (positive) were age, Sequential Organ Failure Assessment Score, Acute Physiology and Chronic Health Evaluation II (APACHE-II) score matched to a cohort of TME patients without EA (control). Univariate analysis compared EA-positive patients against controls. Multivariable logistical regression adjusting for underlying disease etiology was performed to examine the relationship between EA burden and probability of poor neurologic outcome (modified Rankin Score [mRS] 4–6) at discharge. Consecutive admissions to inpatient floors or ICUs that underwent continuous electroencephalography (cEEG) monitoring at a single center between 2012 and 2019. Inclusion criteria were 1) patients with TME diagnosis, 2) age greater than 18 years, and 3) greater than or equal to 16 hours of cEEG. Patients with acute brain injury and cardiac arrest were excluded.

MAIN OUTCOMES AND MEASURES: Poor neurologic outcome defined by mRS (mRS 4–6).

RESULTS: One hundred sixteen patients were included, 58 with EA and 58 controls without EA, where matching was performed on age and APACHE-II score. The median age was 66 (Q1–Q3, 57–75) and median APACHE II score was 18 (Q1–Q3, 13–22). Overall cohort discharge mortality was 22% and 70% had a poor neurologic outcome. Peak EA burden was defined as the 12-hour window of recording with the highest prevalence of EAs. In multivariable analysis adjusted for Charlson Comorbidity Index and primary diagnosis, presence of EAs was associated with poor outcome (odds ratio 3.89; CI [1.05–14.2], $p = 0.041$). Increase in peak EA burden from 0% to 100% increased probability of poor discharge neurologic outcome by 30%.

CONCLUSIONS AND RELEVANCE: Increasing burden of EA is associated with worse discharge outcomes in patients with TME. Future studies are needed to determine whether short-term treatment with anti-seizure medications while medically treating the underlying metabolic derangement improves outcomes.

KEY WORDS: electroencephalogram; encephalopathy; epileptiform abnormalities; toxic-metabolic encephalopathy

Toxic-metabolic encephalopathy (TME) is a diffuse cerebral dysfunction common in critically ill patients that is associated with poor outcomes (1). TME patients can have seizures and a spectrum of electroencephalogram (EEG) patterns known as epileptiform abnormalities (EA), broadly characterized by seizures, and rhythmic and periodic patterns. EA occurs in 50% of critically ill patients and in selected cohorts is associated with morbidity and mortality (2). The clinical significance of these patterns specific to TME is unknown.

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KEY POINTS

Question: To characterize epileptiform abnormality (EA) burden in patients with toxic-metabolic encephalopathy (TME) and its association with morbidity and mortality.

Findings: Retrospective case-control matched study found EA burden was associated with poor outcomes (odds ratio 3.89; CI [1.05–14.2], p = 0.041). Increase in peak EA burden from 0% to 100% increased probability of poor outcome discharge outcome by 30%.

Meaning: Presence of an increasing burden of EA is associated with worse discharge outcomes in patients with TME.

Here, we quantify EA burden in a cohort of TME patients. We subsequently compare TME patients with and without EA and determine the impact of EA burden on neurologic outcome.

MATERIALS AND METHODS

Population and Study Design

This is a retrospective matched cohort analysis of consecutive hospitalized patients undergoing continuous EEG at a single center from 2012 to 2019. The study was approved by the Massachusetts General Hospital Institutional Review Board (IRB protocol number: 2013P001024, 6/2012, "EA in TME") and informed consent was waived by the IRB. Procedures were followed in accordance with the ethical standards of the institutional responsible committee on human experimentation and with the Helsinki Declaration of 1975. The datasets used for cohort identification are institutional collection of sequentially evaluated or admitted patients with acute neurologic problems and includes data extracted from electronic health records (3). Inclusion criteria for our study were adult (age ≥ 18 yr) patients with TME admitted to neurological, medical, and surgical inpatient floors that underwent greater than or equal to 16 hours of continuous EEG. TME was defined as an acute encephalopathy (terms included: "encephalopathy," "altered mental status," "inattentive," "confusion") in the absence of a structural acute brain injury. TME status was determined from inpatient notes and provider assessments. We excluded patients with primary hospitalization for an acute brain injury or cardiac arrest. Patients were required to have at least 16 hours of EEG monitoring, as the likelihood of identifying new EA beyond this window significantly decreases (2).

We defined primary admission diagnosis as: Cardiac: heart failure, acute coronary syndrome, arrhythmias; Respiratory: chronic obstructive pulmonary disease/asthma exacerbations, pneumonia or hypoxia; Renal: acute kidney injury or metabolic disorders (e.g., hyponatremia/hypernatremia, acid-base disorders); Liver: hepatic encephalopathy or liver failure; Other included all other categories such as gastrointestinal disorders (e.g., bleeds), drug/medication intoxication (e.g., cefipime), and urologic conditions (e.g., urinary tract infection, urosepsis).

Data Collection

Clinical and demographic variables and outcomes were previously extracted by members of the study team from electronic health records (2). Any additional data not directly available in the existing datasets, needed for this study were abstracted by the study team from clinical notes and electronic health records. Clinical variables included age, sex, primary non-neurologic admission diagnosis category, previous history of neurologic disease, Acute Physiology and Chronic Health Evaluation (APACHE) II, and Carlson Comorbidity Index, and Sequential Organ Failure Assessment (SOFA) score. Neurologic history and primary neurologic diagnosis were both determined by review of chart records and radiographic data. Patients with missing variables were excluded.

EA patterns were characterized using the American Clinical Neurophysiology Society nomenclature including seizure, lateralized periodic discharges, generalized periodic discharges (GPDs), lateralized rhythmic delta activity (**Fig. 1**) (2, 4). To quantify EA we used a semiautomated extraction, processing, and large-scale labeling method as previously described (2). For the annotation, EEG files were processed and annotated for previous studies (2, 5). We excluded generalized rhythmic delta activity and sporadic discharges from our definition of EA (2). We measured the peak EA burden, defined as maximum EA burden

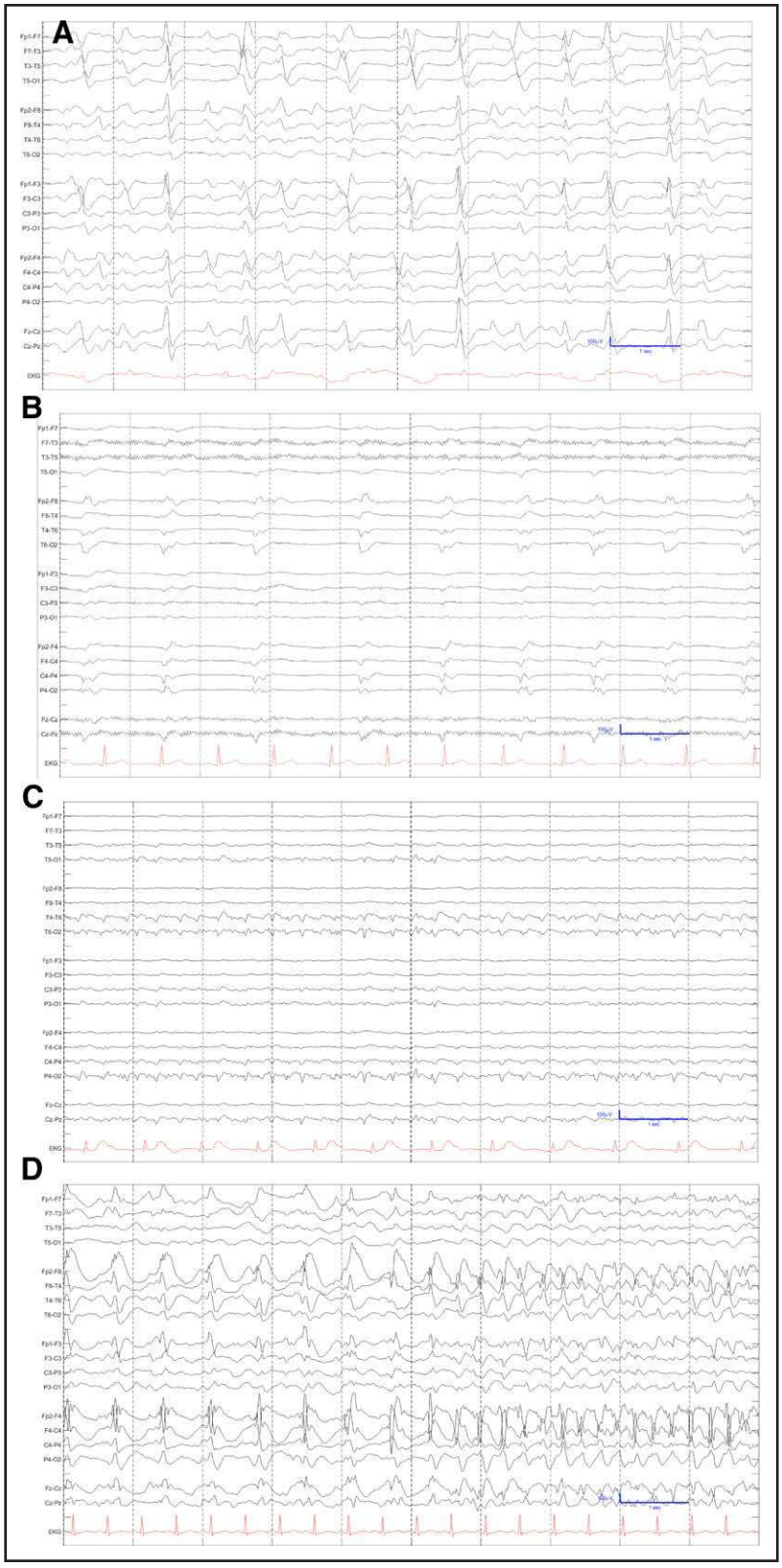

Figure 1. Examples of epileptiform activity are shown. **A**, Generalized periodic discharges. **B**, Lateralized periodic discharges, **C**, Lateralized rhythmic delta activity. **D**, Seizure.

captured within any 12-hour window during the recording (2).

Outcomes were hospital discharge modified Rankin Scale, with poor neurologic outcome being defined as modified Rankin Score (mRS) of 4–6. The discharge outcomes were abstracted directly from notes, when recorded or extrapolated based on clinical examination and extractors were blinded to EA burden as previously described (2).

Statistical Analysis

The final cohort of EA-positive and EA-negative control patients was selected after age, SOFA, and APACHE II score matching. Mann-Whitney *U* and Fischer exact tests were performed to compare continuous and categorical data, respectively. Multivariable regression analysis was performed to compare differences in outcomes between EA-positive patients and EA-negative controls. The regression model included primary diagnosis and Charlson Comorbidity Index. A regression accounting for covariates was performed to demonstrate the dose–response relationship between probability of poor outcome as a continuous function of peak EA. Analysis was performed with R Studio (Boston, MA) and STATA (Chicago, IL).

RESULTS

From the institutional database, we identified 3,041 patients that underwent EEG monitoring. Of these 274 patients met inclusion and exclusion criteria for our study based on their EEG duration and primary admission diagnosis (147 with EA and 127 without EA). We performed manual chart review to confirm eligibility. EA-negative controls were age, SOFA and APACHE-II matched to the EA-positive group with a final cohort of 58 patients in each group. Demographic

and clinical variables are shown in **Supplemental Digital Content 1**, http://links.lww.com/CCX/B189. The median age of the cohort was 66 (IQR 57–75), median Charlson Comorbidity index of 5 (IQR 3–6), and median APACHE II score of 18 (IQR 13–22). Overall discharge mortality was 22% and 71% had a poor mRS outcome.

TME patients with EA had a higher percentage of underlying renal (n = 16 [28%] vs n = 2 [3%], p = 0.01) and liver disease (n = 12 [20%] vs n = 7 [12%], p = 0.001) compared with EA-negative controls. In contrast, controls had more cardiac (n = 12 [21%] vs n = 1 [2%], p = 0.01), and other multisystem conditions such as toxicologic, malignancy, and endocrinologic disorders (n = 17 [29%] vs n = 22 [38%], p = 0.001). There were no significant differences in neurologic history between the two groups and majority of patients did not have a history of neurologic disease. Overall, the EA group had more comorbidities as seen by a higher median Charlson Comorbidity Index (5 IQR 4–6 vs 3 IQR 2–6). There was no significant difference in the frequency of ASM prescription between the two groups. On further review of non-EA patients, ASMs were prescribed for prior history of epilepsy or an initial clinical concern for seizures.

A greater proportion of EA patients (n = 47, 81%) were discharged to nonhome locations or died (rehabilitation, SNF, hospice, death) compared with controls (n = 43, 74%), although the greatest proportion of nonhome discharge locations were short-term care facility (rehabilitation) for EA-positive patients (n = 24, 41%) compared with long-term care facility (skilled nursing facility) (n = 4, 7%). The majority of patients (n = 22, 38%) had a peak EA burden of 10–49%, while 34% (n = 20) of EA patients had a peak EA burden of greater than 50% peak epoch, and only 7% (n = 4) had less than 1% peak EA burden.

On univariate analysis, patients with EA were more likely to have worse neurologic outcomes (mRS 4–6) compared with patients without EA (odds ratio [OR] 3.26 [95% CI, 1.55–6.84], p = 0.0024) (**Table 1**). In a multivariate model adjusting for underlying diagnosis, prior neurological history, and Charlson comorbidity, the presence of EA continued to be significantly associated with poor outcomes (OR 3.89 [95% CI, 1.05––14.2], p = 0.041) (**Table 2**). As the peak EA burden increased from 0% to 100% the probability of poor outcome increased by 30%, after adjusting for covariates (**Fig. 2**). The average marginal effect for this model is an average 0.6% (average marginal effect: 0.006, CI [0.003–0.009], $p \leq 0.001$) increased probability of poor outcome with each 1% increase in peak EA, with the highest rise in probability of poor outcome when burden increases from 20% to 60% (Fig. 2).

Sensitivity and Subgroup Analysis

We performed several sensitivity analyses on the possible effect of comatose status and prior stroke on outcome. EA-positive status remained significantly associated with worse outcomes when adjusting for coma status (GCS ≤ 8; OR 3.95 [95% CI, 1.08–14.5], p = 0.038) and prior stroke (OR 4.22 [95% CI, 1.13–5.77], p = 0.033).

DISCUSSION

In our cohort of TME patients, presence of EA independently increased the odds of a poor outcome. Furthermore, there was a dose-dependent relationship between peak EA burden and poor neurologic outcome, with an average 0.6% increase in probability of poor outcome per percentage increase in peak burden.

Despite being historically seen as a benign entity, TME results in longer hospital lengths of stay and higher mortality compared with general patient populations (1). This is the first study to show within TME specifically, that not only the presence of EAs, but also the burden of EAs may impact outcomes. Our population is unique because we excluded any patients with acute brain injury and anoxic brain injury, in addition there was no significant difference in the frequency of prior neurologic history between our EA-positive patients versus controls. Prior work on the impact of EA on outcomes has shown varying results (6–8). In a cohort with common metabolic disorders, there was a variable presence of EA and no significant EA association with outcomes; however, this review was limited to single case reports and small case series (6). In a large multicenter cohort of 119 COVID-19 patients, EA was found in 48% of patients and increased odds of inpatient seizure, though the effect of EA burden was not investigated (8). A cohort study of 98 patients with severe sepsis found 25% of patients had EA, and that patients with a prior neurologic history were more likely to have EA (7). EA was not associated with

TABLE 1.
Univariate Analysis by Modified Rankin Score Outcome

Covariate	mRS (0–3), *n* = 34	mRS (4–6), *n* = 82	*p*
Age (median, IQR)	57 (43–65)	64 (53–71)	0.061
Acute Physiology and Chronic Health Evaluation II (median, IQR)	15 (11–22)	19 (14–22)	0.0327
Primary diagnosis, *n* (%)			0.027
Cardiac	2	11 (13)	
Respiratory	12	15 (18)	
Renal	1	17 (21)	
Liver	3	16 (20)	
Other	16	23 (28)	
Neurological history present, *n* (%)	14 (41)	29 (35)	0.544
Charlson Comorbidity Index	4 (2–7)	5 (3–6)	0.598
Epileptiform abnormality present, *n* (%)	10 (29)	48 (58)	0.004

IQR = interquartile range, mRS = Modified Rankin Score.

TABLE 2.
Multivariable Analysis by Modified Rankin Score Outcome

Covariate	OR (95% CI)	*p*
Age (median, IQR)	1.04 (1.00–1.07)	0.051
Acute Physiology and Chronic Health Evaluation II (median, IQR)	1.06 (0.97–1.16)	0.179
Primary diagnosis, *n* (%)		
Cardiac	0.84 (0.82–31.5)	0.080
Respiratory	0.72 (0.21–2.51)	0.607
Renal	7.62 (0.77–75.5)	0.083
Liver	8.24 (1.34–50.82)	0.023
Neurological history present, *n* (%)	1.06 (0.77–1.47)	0.716
Charlson Comorbidity Index	0.91 (0.74–1.11)	0.368
Epileptiform abnormality present, *n* (%)	3.89 (1.05–14.2)	0.041

IQR = interquartile range, mRS = Modified Rankin Score, OR = odds ratio.

1-year mortality. Unlike our study, none of these studies of TME patients excluded patients with acute brain injury or cardiac arrest or used TME controls with no EA. Furthermore, in contrast to our study, no previous large study of TME focuses on the dose-dependent effect of EA on outcome.

This study mirrors past findings in subarachnoid hemorrhage (9, 10), ischemic stroke (11), and general inpatients (2) that showed EA burden is associated with poor neurologic outcome. Given EA is seen in a number of pathologies, EA may be a marker of neurologic stress or injury, but it remains unclear if this is "benign" epiphenomena or detrimental to patients. In patients with acute brain injuries (e.g., subarachnoid hemorrhage, trauma), EAs are associated with increased cerebral perfusion and metabolic stress and therefore may result in secondary brain injury (2). Our results support the hypothesis that EA resulting from metabolic disorder may induce cerebral metabolic stress and subsequent brain injury even in the absence of acute structural lesions. The effect of treating EA on long-term outcomes in the TME population is yet to be determined. A previous study on empiric antiseizure medication (ASM) treatment of TME patients with GPDs of triphasic morphology found a clinical response rate of 34% (12). We found no difference in the prescription of ASMs between the two groups, with patients without EA being prescribed ASMs for clinical concerns for seizures. Future studies are indicated to determine whether ASM treatment versus correction of metabolic derangements versus a combination of both improves outcomes in patients with TME and EA.

Limitations of this study include that the data represent a single large metropolitan academic center and a retrospective design. This TME cohort at baseline had high mortality–morbidity, limiting generalizability. We have not evaluated granular data on metabolic derangements due to small numbers that limit power. Similarly, we have not evaluated the impact of different EA subtypes due to small numbers. These need to be studied in future larger studies. We used APACHE II rather than APACHE IV as the former is used as standard of clinical care at our institution. We did not investigate concomitant toxic-metabolic disturbances, longer-term cognitive outcomes, or the impact of ASM treatment on outcomes. Finally, patients in the EA group had higher frequency of withdrawal from life-sustaining therapies. Future studies are needed to

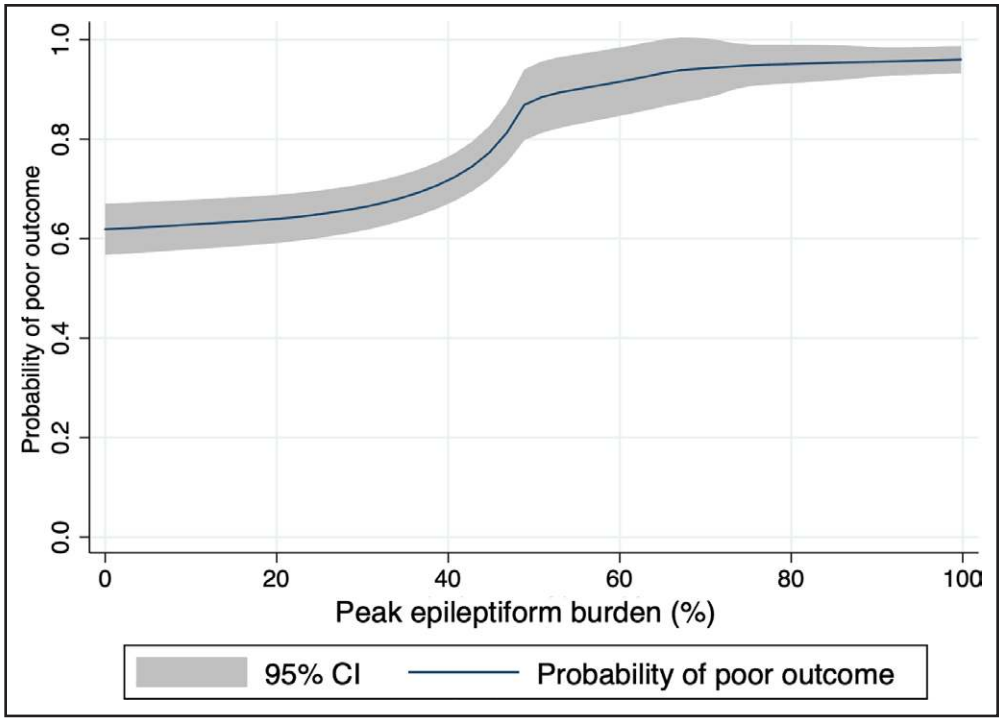

Figure 2. Dose-response relationship between peak epileptiform abnormality (EA) burden and probability of poor outcome (modified Rankin Score 4–6). Baseline probability of poor outcome without EA was 65%. A peak EA burden increase from 0% to 100% increases the probability of poor outcome by 30%, with the steepest increase when peak increases from 20% to 60%.

determine whether treatment with ASM versus correction of underlying metabolic derangement is more likely to improve outcomes.

CONCLUSIONS

In a cohort of TME patients, EA presence and peak burden are independently associated with poor neurologic outcome. Our findings highlight the importance of future prospective studies to understand the effect of and interaction between ASMs and the correction of metabolic derangements, on long-term outcomes of TME patients with EA.

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REFERENCES

1. Frontera JA, Melmed K, Fang T, et al: Toxic metabolic encephalopathy in hospitalized patients with COVID-19. *Neurocrit Care* 2021; 35:693–706
2. Zafar SF, Rosenthal ES, Jing J, et al: Automated annotation of epileptiform burden and its association with outcomes. *Ann Neurol* 2021; 90:300–311
3. Amerineni R, Sun H, Lee H, et al: Using electronic health data to explore effectiveness of ICU EEG and anti-seizure treatment. *Ann Clin Transl Neurol* 2021; 8:2270–2279
4. Hirsch LJ, LaRoche SM, Gaspard N, et al: American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. *J Clin Neurophysiol* 2013; 30:1–27
5. Jing J, Ge W, Struck AF, et al: Interrater reliability of expert electroencephalographers identifying seizures and rhythmic and periodic patterns in electroencephalograms. *Neurology* 2023; 100:e1737–e1749
6. Faigle R, Sutter R, Kaplan PW: Electroencephalography of encephalopathy in patients with endocrine and metabolic disorders. *J Clin Neurophysiol* 2013; 30:505–516
7. Gilmore EJ, Gaspard N, Choi HA, et al: Acute brain failure in severe sepsis: A prospective study in the medical intensive care unit utilizing continuous EEG monitoring. *Intensive Care Med* 2015; 41:686–694
8. Lin L, Al-Faraj A, Ayub N, et al: Electroencephalographic abnormalities are common in COVID-19 and are associated with outcomes. *Ann Neurol* 2021; 89:872–883
9. Zafar SF, Rosenthal ES, Postma EN, et al: Antiseizure medication treatment and outcomes in patients with subarachnoid hemorrhage undergoing continuous EEG monitoring. *Neurocrit Care* 2022; 36:857–867

10. Kim JA, Rosenthal ES, Biswal S, et al: Epileptiform abnormalities predict delayed cerebral ischemia in subarachnoid hemorrhage. *Clin Neurophysiol* 2017; 128:1091–1099
11. Tabaeizadeh M, Aboul Nour H, Shoukat M, et al: Burden of epileptiform activity predicts discharge neurologic outcomes in severe acute ischemic stroke. *Neurocrit Care* 2020; 32:697–706
12. O'Rourke D, Chen PM, Gaspard N, et al: Response rates to anticonvulsant trials in patients with triphasic-wave EEG patterns of uncertain significance. *Neurocrit Care* 2016; 24:233–239