# Effects of epileptiform activity on discharge outcome in critically ill patients in the USA: a retrospective cross-sectional study

*Harsh Parikh*, Kentaro Hoffman*, Haoqi Sun*, Sahar F Zafar*, Wendong Ge, Jin Jing, Lin Liu, Jimeng Sun, Aaron Struck, Alexander Volfovsky†, Cynthia Rudin†, M Brandon Westover†*

## Summary

**Background** Epileptiform activity is associated with worse patient outcomes, including increased risk of disability and death. However, the effect of epileptiform activity on neurological outcome is confounded by the feedback between treatment with antiseizure medications and epileptiform activity burden. We aimed to quantify the heterogeneous effects of epileptiform activity with an interpretability-centred approach.

**Methods** We did a retrospective, cross-sectional study of patients in the intensive care unit who were admitted to Massachusetts General Hospital (Boston, MA, USA). Participants were aged 18 years or older and had electrographic epileptiform activity identified by a clinical neurophysiologist or epileptologist. The outcome was the dichotomised modified Rankin Scale (mRS) at discharge and the exposure was epileptiform activity burden defined as mean or maximum proportion of time spent with epileptiform activity in 6 h windows in the first 24 h of electroencephalography. We estimated the change in discharge mRS if everyone in the dataset had experienced a specific epileptiform activity burden and were untreated. We combined pharmacological modelling with an interpretable matching method to account for confounding and epileptiform activity–antiseizure medication feedback. The quality of the matched groups was validated by the neurologists.

**Findings** Between Dec 1, 2011, and Oct 14, 2017, 1514 patients were admitted to Massachusetts General Hospital intensive care unit, 995 (66%) of whom were included in the analysis. Compared with patients with a maximum epileptiform activity of 0 to less than 25%, patients with a maximum epileptiform activity burden of 75% or more when untreated had a mean 22·27% (SD 0·92) increased chance of a poor outcome (severe disability or death). Moderate but long-lasting epileptiform activity (mean epileptiform activity burden 2% to <10%) increased the risk of a poor outcome by mean 13·52% (SD 1·93). The effect sizes were heterogeneous depending on preadmission profile—eg, patients with hypoxic-ischaemic encephalopathy or acquired brain injury were more adversely affected compared with patients without these conditions.

**Interpretation** Our results suggest that interventions should put a higher priority on patients with an average epileptiform activity burden 10% or greater, and treatment should be more conservative when maximum epileptiform activity burden is low. Treatment should also be tailored to individual preadmission profiles because the potential for epileptiform activity to cause harm depends on age, medical history, and reason for admission.

**Funding** National Institutes of Health and National Science Foundation.

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*Lancet Digit Health* 2023; 5: e495–502

Published Online June 7, 2023 https://doi.org/10.1016/S2589-7500(23)00088-2

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*Co-first authors

†Co-senior authors

**Department of Computer Science, Duke University, Durham, NC, USA** (H Parikh PhD, A Volfovsky PhD, Prof C Rudin PhD); **Deptartment of Statistics and Operation Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA** (K Hoffman PhD); **Department of Neurology, Massachusetts General Hospital, Boston, MA, USA** (H Sun PhD, S F Zafar MD, W Ge PhD, J Jing PhD, Prof M B Westover MD PhD); **Department of Epidemiology, Harvard T H Chan School of Public Health, Boston, MA, USA** (L Liu PhD); **The Grainger College of Engineering, University of Illinois Urbana-Champaign, Urbana-Champaign, IL, USA** (Prof J Sun PhD); **Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA** (A Struck MD); **Institute of Natural Sciences, MOELSC, School of Mathematical Sciences and SJTU-Yale Joint Center for Biostatistics and Data Science, Shanghai Jiao Tong University, Shanghai, China** (L Liu)

Correspondence to: Prof M Brandon Westover, Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA **mwestover@mgh.harvard.edu**

## Introduction

Epileptiform activity (also known as ictal–interictal–injury continuum activity[1]) is common in critically ill patients, affecting more than half of patients who undergo electroencephalography (EEG) in critical care.[2–5] Epileptiform activity varies in terms of spatial extent (generalised *vs* lateralised) and periodicity (periodic *vs* rhythmic *vs* sporadic). Here, we consider epileptiform activity to be the combination of seizures, lateralised periodic discharges, generalised periodic discharges, and lateralised rhythmic delta activity. Prolonged epileptiform activity is associated with in-hospital mortality, and survivors often have long-term functional and cognitive disability.[6–9] Despite a growing literature indicating epileptiform activity is associated with poor outcomes,[10] there is a long-standing debate about whether epileptiform activity is part of a causal pathway that worsens outcomes and thus requires aggressive treatment, or whether worsened outcomes are due to mechanisms other than epileptiform activity, such as medication side-effects or the inciting illness, with epileptiform activity as an epiphenomenon.[11–16]

Studies of the effects of epileptiform activity on neurological outcomes have a variety of limitations. First, a hypothetical clinical trial studying the effect of untreated epileptiform activity would compare outcomes in groups

## Research in context

### Evidence before this study

We searched PubMed for articles published between Jan 1, 2005, and Dec 31, 2021, using the search terms: "(epilep* OR (ictal AND (interictal OR inter-ictal) AND continu*) OR (eletrogra* AND seizure)) AND (activity OR discharge) AND ((critic* AND ill) OR (intens* AND care)) AND outcome" in the title or abstract, and "medication OR drug" in all fields. We limited the results to human studies, published in English, and with full text available. Several studies have established associations between epileptiform activity and neurological outcomes. However, these studies failed to adjust for short-term and long-term effects of antiseizure medications. Not adjusting for treatment is problematic because several recent studies suggest aggressive antiseizure medication use, especially intravenous anaesthetic drugs such as propofol, might be harmful. However, adjusting for these factors is challenging because of the complex interactions and feedback between epileptiform activity and antiseizure medications. Yet, without adjusting for these factors, it remains unclear whether associations between epileptiform activity and poor outcomes are due to over-treatment, underlying illness, or effects of epileptiform activity. Whether aggressive treatment is needed has been a subject of debate in the field without a definitive answer.

### Added value of this study

Using a novel causal inference approach and auditing by neurologists, our results show that epileptiform activity burden worsens neurological outcomes after disentangling the interaction between epileptiform activity and antiseizure medication. However, the effect depends on the pattern of epileptiform activity (maximum and average epileptiform activity burden).

### Implications of all the available evidence

An optimal personalised treatment policy is needed that puts a higher priority on patients with a high mean epileptiform activity burden, while being more conservative when maximum epileptiform activity burden is low.

of patients who have different levels of epileptiform activity burden but are otherwise matched for relevant clinical variables, while ensuring no antiseizure medications are administered, which is neither possible nor ethical. Second, observational data contain complex interactions of epileptiform activity and antiseizure medications—ie, physicians administer antiseizure medications on the basis of the patient's epileptiform activity, and in turn, epileptiform activity is affected by antiseizure medications. This creates entanglement (figure 1) between epileptiform activity and antiseizure medications, obscuring the true effect of epileptiform activity. Furthermore, observational datasets are subject to unmeasured confounding. Therefore, a naive statistical analysis without appropriately adjusting confounding can lead to both high bias and variance. Previous studies of epileptiform activity have used regression models to adjust for medical history and demographic factors[7–9,17] and interpreted the regression coefficient for epileptiform activity as the effect of epileptiform activity on the outcome. Although this approach is appealing for its simplicity, the interpretation of regression coefficients can be misleading due to epileptiform activity–antiseizure medication interactions. On the other hand, relying on data-driven black-box machine learning models for such analyses can lead to uninterpretable conclusions and difficult clinical validation.

See Online for appendix

Our objective was to quantify the heterogeneous effects of epileptiform activity with an interpretability-centred approach in which a physician can verify the quality of every analysis step, including how a current patient compares with others (case-based reasoning), how drug absorption and response is modelled, and the relative importance of covariates. We leveraged the domain knowledge using pharmacokinetic–pharmacodynamic models to describe the interactions between clinical decisions and physiological response, which identifies individuals who react similarly to treatments. We used a matching method to estimate both medium and long-term effects of clinical decisions and physiological responses. The matched group constructed for each patient can be validated via chart review.

## Methods

### Study design and participants

We did a retrospective, cross-sectional study of patients in the intensive care unit who were admitted to Massachusetts General Hospital (Boston, MA, USA). Participants were aged 18 years or older and had electrographic epileptiform activity identified by a clinical neurophysiologist or epileptologist who read the reports of EEG findings in the electronic health record of Massachusetts General Hospital. Patients were excluded if their EEG quality was low (where the duration of consecutive artifact [defined in the appendix p 3] was more than 30% of the total length); if they had less than 2 h of continuous EEG monitoring; and if they had missing outcomes or covariates (appendix p 3). The results are reported in accordance with the STROBE guidelines for reporting observational studies.[18] Institutional review boards at Massachusetts General Hospital, Duke University, and University of North Carolina at Chapel Hill approved the analysis without requiring written informed consent.

### Outcomes

The outcome was the modified Rankin Scale (mRS) abstracted from physician and physical therapy notes at

hospital discharge. The mRS was abstracted retrospectively and adjudicated by independent reviewers, who were masked to EEG or the antiseizure medications status. The outcome was the modified Rankin Scale (mRS) at hospital discharge. The mRS is a 0–6 ordinal scale where 0 means no symptoms and 6 means the patient has died. We dichotomised mRS into poor (mRS ≥4: moderately severe disability) and favourable (mRS ≤3: moderate disability) outcomes.[9] Patients with missing discharge mRS data were excluded. The outcome adjudicators were masked to epileptiform activity status and burden.

## Exposures

The exposure was epileptiform activity burden. Epileptiform activity is defined as one of four patterns:[1] generalised periodic discharges, lateralised periodic discharges, lateralised rhythmic delta activity, and seizure. The mean duration of EEG per patient was 27·25 h (SD 5·63). Every 2 s EEG segment was classified as containing epileptiform activity or not by a deep neural network (appendix p 20) using an automated algorithm that was developed to detect these key intensive care unit EEG patterns (rather than relying on EEG reports). Then, a timeseries was generated as the fraction of 2 s EEG segments containing epileptiform activity over a 6 h window. We chose 6 h to observe the effects of antiseizure medications on epileptiform activity and for physicians to adjust antiseizure medication treatment. Epileptiform activity burden was defined in two clinically meaningful ways: (1) $EA_{mean}$ measures the mean epileptiform activity fraction among all 6 h sliding windows (step size of 10 min) within the first 24 h of EEG; and (2) $EA_{max}$ measures the maximum epileptiform activity fraction among all 6 h sliding windows within the first 24 h of EEG. By quantifying epileptiform activity burden in these two ways, we sought to separate potentially different effects of intense but brief epileptiform activity ($EA_{max}$) from prolonged periods of less intense epileptiform activity ($EA_{mean}$). For interpretability and statistical efficiency, we binned $EA_{max}$ burden into mild (0% to <25%), moderate (25% to <50%), severe (50% to <75%), and very severe (75% to <100%) and we binned $EA_{mean}$ into mild (0% to <2%), moderate (2% to <10%), severe (10% to <30%), and very severe (30% to <100%). As for epileptiform activity, we binned each administered antiseizure medication into two groups: minimal or low and clinically significant. Groups were chosen as a function of the estimated median dose required to reduce epileptiform activity burden by 50% ($ED_{50}$) across the patient population. Here, for a particular antiseizure medication, a patient's treatment with that medication was considered minimal if the mean dose of that for the patient was less than one tenth of the population median $ED_{50}$, otherwise it was considered clinically significant. If all antiseizure medications administered for each patient were in the minimal category then we characterised that patient's overall antiseizure medication regimen as untreated. Otherwise, if any antiseizure medication administration was clinically significant then the patient was considered treated with antiseizure medication. A sensitivity analysis of these design choices is shown in the appendix (p 28). The sensitivity analysis aimed to study how sensitive the results were to unmeasured confounding, imprecision in epileptiform activity quantification, and the choice of bins.

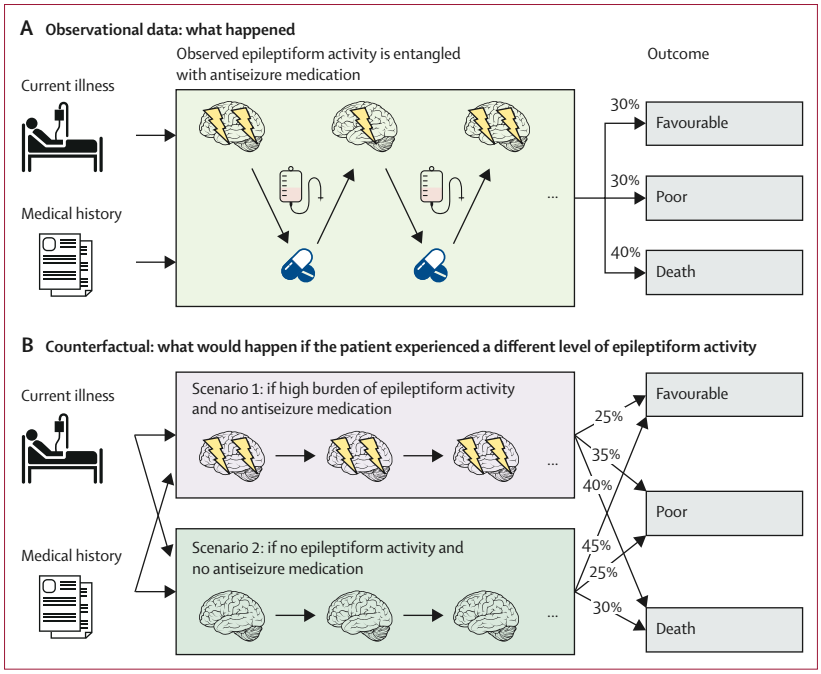


***Figure 1:*** **Illustration of observed and counterfactual scenarios in the intensive care unit**
(A) Observed epileptiform activity forms a feedback loop with treatment decisions that are also influenced by current illness and medical history. The entire time-series of epileptiform activity and antiseizure medication influence patient outcomes. Possible outcomes include favourable, poor, or death at the time of hospital discharge. (B) Estimating the counterfactual case: scenarios in which the patient had a different level of epileptiform activity effect.

## Covariates

The covariates were preadmission variables and drug responsiveness. For each patient we observed 70 covariates denoted as preadmission variables, covering demographics (age, sex, and marital status), clinical factors (including history of seizures or epilepsy and chronic kidney disease), and admission diagnosis (including cancer and subarachnoid haemorrhage). They are denoted as the pre-admission variables. The full list of preadmission variables are listed in the appendix (p 3). Patients with missing covariates were excluded. Patient sex and race or ethnicity were extracted from the hospital electronic health record.

The second source of confounding came from the patients' drug responsiveness. Due to differing medical history, medical conditions, age, and so on, patients might respond differently to antiseizure medications. The antiseizure medications studied here were

lacosamide, levetiracetam, midazolam, pentobarbital, phenobarbital, propofol, valproate, lorazepam, diazepam, and combined phenytoin and fosphenytoin. Although other antiseizure medications are sometimes used and can be effective in treating epileptiform activity, their use was much less frequent in our cohort. To account for this, we modelled each patient's response to antiseizure medication via one-compartment pharmacokinetic models and the Hill equation for pharmacodynamic response. For the pharmacokinetic model, the half-lives of antiseizure medications were obtained from drug databases and fixed (appendix p 7). For the pharmacodynamic model, the Hill coefficient and the dose required to reduce $ED_{50}$ represent the patient's drug responsiveness for each antiseizure medication and were estimated from the data. Estimation of per-patient pharmacodynamic models allowed adjusting for heterogeneity of drug-response and drug-effectiveness (ie, the effect on epileptiform activity burden).

We did not explicitly model drug interactions to avoid curse of dimensionality issues. Nevertheless, most of the antiseizure medications used in our cohort were levetiracetam, lacosamide, and propofol, for which interactions are minimal, and antiseizure medications known to interact were rare in our study. Because our study focuses on the time that patients were on EEG, pharmacokinetic–pharmacodynamic changes are likely to be small. Patients with missing EEG or antiseizure medication data were not included in the analyses.

### Effect estimation through matching

We aimed to estimate the degree to which untreated epileptiform activity worsens neurological outcomes. Our estimand was the probability of a poor outcome if the patient has epileptiform activity burden ($EA_{max}$ or $EA_{mean}$) equal to a given level in the absence of treatment. We studied this counterfactual outcome (what would have happened without antiseizure medication) because it disentangles the effects of epileptiform activity from antiseizure medication on outcomes.

The covariates, including age, demographics, clinical factors such as disease histories and medical diagnoses, and drug response parameters, were used for matching: each patient was matched to patients with similar covariates. We used an interpretable distance metric-based matching algorithm, Matching After Learning To Stretch,[19] to match patients directly on covariates (not on proxies as with propensity scores). The resulting matched groups permitted case-based reasoning and allowed estimating the heterogeneous effects of both epileptiform activity and drugs on outcomes. The overall analysis framework is shown in figure 2. We conducted subset analyses. The subgroups were based on various neurological conditions, chosen a priori on the basis of patients' history and diagnosis.

Inspired by similar approaches in the social sciences,[20] one can check for unobserved confounders by having a domain expert perform a post-facto analysis of matched groups. Three independent neurologists (MBW, SZ, and AS) were sent three randomly chosen matched groups for manual chart review to assess matching quality and determine unmeasured confounding. Reviewers were asked to independently perform a qualitative analysis of the matched groups and report the estimated chance of having a high epileptiform activity burden and the chance of a poor outcome (estimates were grouped into 0% to <20%, 20% to <40%, 40% to <60%, 60% to <80%, and 80% to 100%). A validation was judged as successful if (1) in the clinician's judgement, the patients in the matched groups were medically similar—ie, the matched group was tight; and (2) the outcome prognosis and epileptiform activity propensity were similar. A validation was judged to have failed if the reviewing clinicians found a clinically significant medical difference in either outcome prognosis or epileptiform activity propensity that, in the clinicians' judgement, would invalidate the matching group. The tightness of the matched groups was important for validation. The tighter the matched groups, the more the study would resemble a randomised control trial with matched treatment and control patients. The validity of the effect estimation depends on the validity of the matching groups. Our physicians evaluated a random subset of three matched groups using clinical notes (hospital admission summaries). These clinical notes (and the information in them) were not explicitly used by our method for matching; they were only used as

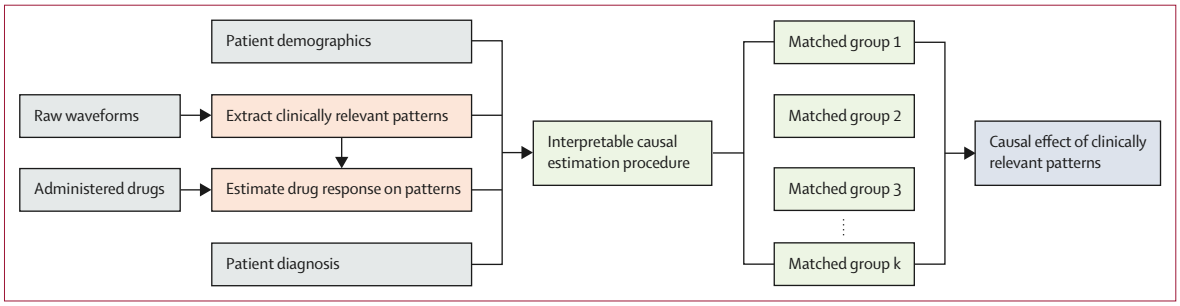


***Figure 2:*** **The overall analysis framework**
The analysis framework consists of four parts (indicated by different colours): epileptiform activity burden computation, individual pharmacokinetic–pharmacodynamic modelling, Matching After Learning to Stretch, and effect estimation.

an independent method for evaluating the validity of the matched groups. This allowed the physician reviewers to reason about the existence of any important unobserved confounders that could invalidate the analysis.

### Statistical analysis

Continuous data are presented as mean (SD). Categorical data are presented using number and percentage. Confidence intervals were derived via bootstrapping, by randomly sampling the same number of patients with replacement 1000 times and computing lower and upper bounds as the 2·5% and 97·5% percentiles of the bootstrapped results.

Sensitivity analysis was conducted in terms of unobserved confounding and imprecision in epileptiform activity burden, by varying the strength of unobserved confounding and noise in the epileptiform activity burden. Details of the sensitivity analysis are described in the appendix (pp 18–24). Python version 3.9.7 was used for analyses.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Between Dec 1, 2011, and Oct 14, 2017, 1514 patients were admitted to Massachusetts General Hospital intensive care unit, 995 (66%) of whom were included in the analysis. Eight (1%) patients were excluded due to missing discharge mRS data, 314 (21%) were excluded due to missing covariates, and 197 (13%) were excluded because their EEG quality was low or they had less than 2 h of continuous EEG monitoring (appendix p 3). Preadmission patient characteristics are shown in the table. We found no significant difference between the mean dichotomised discharge mRS for patients with and without missing EEG data (p=0·39; appendix p 23).

Patients with higher levels of $EA_{max}$ were at higher risk of poor neurological outcomes (figure 3A). Moreover, the risk of a poor outcome increased monotonically as epileptiform activity burden increased, culminating in a mean increase of 22·27% (SD 0·92) when a patient's untreated epileptiform activity burden increased from mild (0% to <25%) to very severe (75% to 100%). Patients with higher $EA_{mean}$ were also at higher risk of a poor outcome (figure 3B). Similar to $EA_{max}$, the risk increased monotonically with increase in epileptiform activity burden. Our results indicate that severe and very severe epileptiform activity burden of longer than 24 h increase the risk of a poor outcome by mean 17·97% (SD 1·93) compared with mild prolonged epileptiform activity burden. Moderate but long-lasting epileptiform activity (mean epileptiform activity burden 2% to <10%) increased the risk of a poor outcome by mean 13·52% (SD 1·93).

| | Participants (n=995) |
|---|---|
| **Major covariates included as confounders*** | |
| Age, years | 61 (48–73) |
| Sex | |
| Male | 475 (48%) |
| Female | 520 (52%) |
| Race | |
| Asian | 33 (3%) |
| Black or African American | 72 (7%) |
| White | 751 (75%) |
| Other | 50 (5%) |
| Unavailable or declined | 84 (8%) |
| Premorbid mRS before admission | 0 (0–3) |
| APACHE II score in first 24 h after admission | 19 (11–25) |
| Initial Glasgow Coma Scale score | 11 (6–15) |
| **Exposure** | |
| Epileptiform activity burden, $EA_{max}$ | 0·65 (0·16–0·99) |
| Epileptiform activity burden, $EA_{mean}$ | 0·09 (0·01–0·31) |
| **Outcome** | |
| Discharge mRS | 4 (4–5) |

Data are median (IQR) or n (%). APACHE II scores range from 0 to 71, with higher scores corresponding to more severe disease and a higher risk of death. $EA_{max}$=the maximum epileptiform activity fraction among all 6 h sliding windows within the first 24 h of EEG. APACHE II=Acute Physiology and Chronic Health Evaluation II. $EA_{mean}$=the mean epileptiform activity fraction among all 6 h sliding windows (step size of 10 min) within the first 24 h of EEG. mRS=modified Rankin Scale. *Full list of covariates in appendix p 3.

*Table:* **Patient characteristics**

We then studied the effect heterogeneity in various subgroups. Our results suggest that patients with hypoxic-ischaemic encephalopathy or acquired brain injury were at higher risk of a worse outcome in response to a large $EA_{max}$, possibly attributable to inflammation leading to exacerbated harm of neurological injury (figure 4). These findings suggest potential effect modification by many different types of pathology, although in most cases our results were not statistically significant, given the size of the subgroups. We also examined race and sex as possible effect modifiers of epileptiform activity burden (data not shown); however, these factors did not modify the risk from $EA_{max}$.

Matching After Learning to Stretch (MALTS) is a matching method that estimates heterogeneous causal effects via distance metric learning augmented matching. For $EA_{max}$, two measures of illness severity were heavily weighted (worst Glasgow Coma Scale score in first 24 h and Acute Physiology and Chronic Health Evaluation II [APACHE II] score; appendix p 13). Levetiracetam pharmacodynamics ($ED_{50}$ and Hill coefficient) and diastolic blood pressure were the other most important variables. These observations suggest that our matched groups consist of individuals with similar overall health, current level of neurological impairment, and their responsiveness to important non-sedating anti-epileptic drugs. The three least important matching variables were

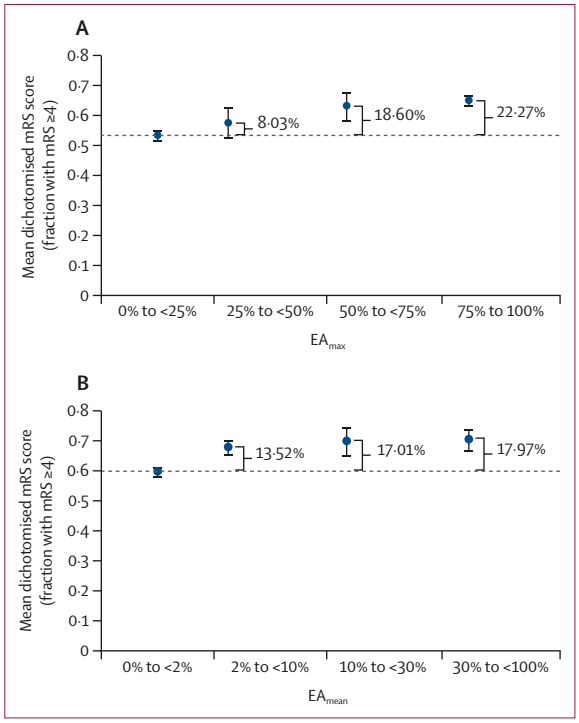


***Figure 3:*** **The probability of a poor outcome mRS for patients with mild, moderate, severe, or very severe epileptiform activity burden**
(A) Mean dichotomised mRS (fraction of patients with mRS ≥4) in response to epileptiform activity burden quantified as $EA_{max}$. (B) Mean dichotomised mRS (fraction of patients with mRS ≥4) in response to epileptiform activity burden quantified as $EA_{mean}$. In both scenarios, an increase in epileptiform activity burden led to a worse potential outcome. Outcome worsened monotonically for $EA_{max}$, whereas for $EA_{mean}$, there was an increase at approximately 2%. In both plots, the horizontal line represents the baseline median average potential outcome for the mild case. $EA_{max}$=the maximum epileptiform activity fraction among all 6 h sliding windows within the first 24 h of EEG. $EA_{mean}$=the mean epileptiform activity fraction among all 6 h sliding windows (step size of 10 min) within the first 24 h of EEG. mRS=modified Rankin Scale.

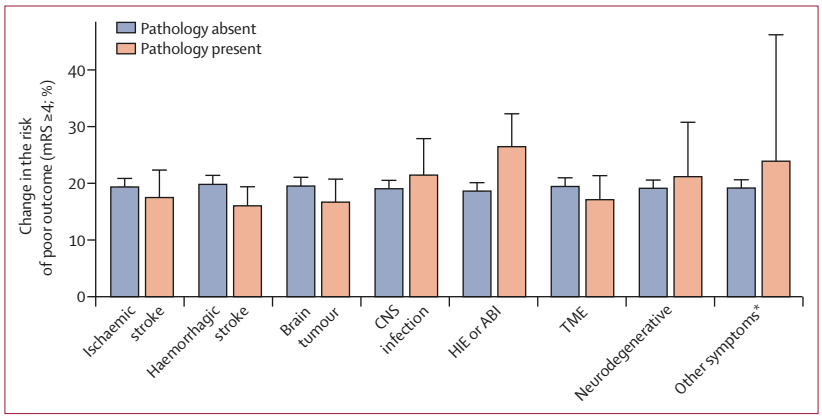


***Figure 4:*** **Heterogeneity in the effects of $EA_{max}$**
The causal effects of epileptiform activity are stratified by various central nervous system pathologies. The blue bars represent causal effects when a particular pathology is absent and the red bars represent conditional causal effects when that pathology is present. ABI=acquired brain injury. $EA_{max}$=the maximum epileptiform activity fraction among all 6 h sliding windows within the first 24 h of EEG. HIE=hypoxic–ischaemic encephalopathy. mRS=modified Rankin Scale. TME=toxic-metabolic encephalopathy. *Symptoms that are suspected to be epilepsy related.

Hill coefficients and $ED_{50}$ parameters from one of the antiseizure medications (appendix p 13). This stands in contrast with $ED_{50}$ for levetiracetam, one of the top five most important variables, suggesting that information about responsiveness to levetiracetam, a potent non-sedating antiseizure drug, is more relevant in estimating effects of epileptiform activity on outcome than other less potent antiseizure medications.

To ensure the validity of our approach, the neurologists found no problematic sources of confounding in the matched groups (appendix p 14). Moreover, we observed which factors each group was matched tightly on. For example, group 2 was tightly matched, with patients having similar initial Glasgow Coma Scale and APACHE II scores and all but one having relatively good prognoses. By contrast, group 3 was tightly matched on acute neurological injuries at the cost of a looser match on APACHE II scores. Viewing what is tightly matched in each group provides a holistic evaluation of the factors controlled for (eg, age) and the factors either unimportant or with small sample size (eg, many of the less common medical conditions). For further validation, see the sensitivity analysis results in the appendix (pp 18–24).

## Discussion

Our findings have two primary implications for treatment of epileptiform activity. First, treatment should be based on both $EA_{max}$ and $EA_{mean}$. Intense bursts of epileptiform activity burden (captured by $EA_{max}$), even if relatively brief (6 h), lead to worse outcomes. Similarly, sustained periods of epileptiform activity (captured by $EA_{mean}$) show a monotonic relationship with the outcome: epileptiform activity less than 2% has minimal effect, but any epileptiform activity of 2% to less than 10% increases the risk of a worse outcome at least by 13·52% (SD 1·93). This suggests interventions should put a higher priority on patients with a mean epileptiform activity burden higher than 10%, while treatment should be more conservative when maximum epileptiform activity burden is low. Second, treatment should be tailored to individual preadmission profiles because the potential for epileptiform activity to cause harm depends on age, medical history, and reason for admission. By contrast, current treatment protocols tend to be generic and based on the duration of epileptiform activity but provide little guidance on how to consider other patient characteristics. As a result, treatment approaches vary widely between doctors. Our results suggest that future, larger sample studies should be designed to better understand the heterogeneity of effects of epileptiform activity for patients with different CNS pathologies.

Our work builds on previous studies showing associations between epileptiform activity, treatments, and neurological outcomes. Oddo and colleagues[10] studied 201 patients admitted to the intensive care unit, 120 (60%) of whom had sepsis as an admission diagnosis.

The authors found that epileptiform activity (seizures and periodic discharges) was associated with worse outcomes based on a regression adjustment for age, coma, circulatory shock, acute renal failure, and acute hepatic failure. However, they did not adjust for treatment with antiseizure medications, including phenytoin (given to 14 [67%] of 21 patients with electrographic seizures, similar to epileptiform activity), levetiracetam (13 [62%] patients), and lorazepam (12 [57%] patients), and four other drugs. Tabaeizadeh and colleagues[21] found that the maximum daily burden of epileptiform activity or seizures was associated with a higher risk of poor outcomes in 143 patients with acute ischaemic stroke. However, the authors did not control for antiseizure medications, which were given to 56 (83%) of 67 patients. Paediatric studies on epileptiform activity also have not adjusted for drug use.[6] Not adjusting for treatment is problematic because a growing number of studies suggest aggressive antiseizure medication use, especially with intravenous anaesthetic drugs (such as propofol), might be harmful. For example, a retrospective study by Marchi and colleagues[22] of 467 patients with incident status epilepticus found that therapeutic coma was associated with poorer outcomes, higher prevalence of infection, and longer hospital stay.[23,24] However, because more aggressive treatment is reserved for more severely ill patients, these studies have come under criticism for failing to adequately adjust for the type and severity of medical illness, and for the burden of epileptiform activity.

The monotonic relationship between epileptiform activity burden and poor outcome has been suggested by multiple studies.[6] Our study supports these findings and suggests a high likelihood of a causal relationship. We expect a causal relationship to be generalisable, particularly because previous studies have found a similar relation between epileptiform activity burden and outcomes in disease subgroups included in our study (eg, stroke, cardiac arrest, non-neurological medical and surgical patients, and in distinct populations not included in our work such as paediatric patients in the intensive care unit[6]). Although randomised trials are challenging to conduct, alternative epidemiological approaches could be used to test the results in an independent dataset.

A key component of our approach is adjusting for patients' drug responsiveness (pharmacokinetic and pharmacodynamic parameters) to account for patient heterogeneity. Critically ill patients can be different in many ways, including measured and unmeasured variables. By accounting for individual drug responsiveness, we were able to adjust for exposure to antiseizure medications, such as phenytoin and pentobarbital, where the medications themselves might worsen outcomes. Another advance is our application of a methodology designed specifically for causal inference using observational data. The matching approach in MALTS achieves both the flexibility of being free of model misspecification (non-parametric) and the interpretability of the estimated weights, creating less biased effect estimates. With this new approach, we provide credible estimates of how much harm epileptiform activity causes and in which types of patients.

Our approach has several limitations. Although we have conducted sensitivity analysis, this does not change the retrospective cross-sectional nature of the study. Therefore, there are still unmeasured confounding factors, such as illness present before admission, which were not captured in our data and positively contribute to both having high epileptiform activity burden and a poor outcome. Delirium can be a cause of lower Glasgow Coma Scale score; however, it was not routinely assessed in the intensive care unit of our cohort. When evaluating epileptiform activity burden, we did not consider the subtype of epileptiform activity (generalised periodic discharges, lateralised periodic discharges, lateralised rhythmic delta activity, or seizure), discharge frequency, or the spatial extent of epileptiform activity. Furthermore, because bilateral independent periodic discharges are rare, the raters in our study labelled these as generalised periodic discharges. Our pharmacokinetic–pharmacodynamic model could be improved by including more mechanistic or physiological detail, such as learning heterogeneous pharmacokinetic parameters across patients, adjusting for changes in pharmacokinetic–pharmacodynamic parameters over the course of treatment, drug interactions, and context-sensitive half-life for propofol.[25] In addition, the deep learning model that detects epileptiform activity patterns is not perfect (appendix p 20), even though the result is robust to systematic shift in the model output probability (appendix p 28). The current study also did not estimate an optimal treatment policy to improve patient outcomes, which is an important future research direction. We hope to organise an international data sharing collaboration in the near future to make further progress on this important topic. An ideal observational cohort will have at least three important properties: a large size, because a larger dataset would allow testing for effect heterogeneity across various etiopathogenesis; a multicentre design, which would allow for greater variation in practice patterns; and additional information such as detailed annotation based on epileptiform activity subtypes, potential confounders, and effect modifiers over the course of treatment.

**Contributors**

HP, KH, HS, AV, CR, and MBW conceptualised the study. WG, JJ, SFZ, and MBW curated the data. WG and JJ developed the neural network model for detecting epileptiform activity in raw EEG data. HP, KH, and HS analysed the data. MBW and JS acquired funding. HP, KH, HS, AV, CR, and MBW created the methodology. AV, CR, and MBW gave supervision. AS, SFZ, and MBW performed chart review on the matched groups. HS, SFZ, and MBW accessed and verified the data. HP, KH, and HS created the figures. HP, KH, HS, AV, CR, and MBW wrote the original draft. All authors reviewed and edited the final manuscript. All authors had access to raw data and had final responsibility for the decision to submit for publication.

### Declaration of interests

MBW is a co-founder of Beacon Biosignals, which played no role in this study. SFZ is a clinical neurophysiologist consultant for Corticare. All other authors declare no competing interests.

### Data sharing

Written requests for access to the data reported in this paper will be considered by the corresponding author and a decision made about the appropriateness of the use of the data. If the use is appropriate, a data-sharing agreement will be put in place before a fully de-identified version of the dataset used for the analysis with individual patient data is made available.

### Acknowledgments

MBW is supported by National Institutes of Health grants R01NS102190, R01NS102574, R01NS107291, RF1AG064312, RF1NS120947, and R01AG073410. CR, AV, and HP are supported by the National Science Foundation grant IIS-2147061 and AV is supported by the National Science Foundation grant DMS-2046880.

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