**Understanding the Harm Caused by Epileptiform Activity in Critically Ill Patients**

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| **Research in context**  **Evidence before this study**  Several prior studies have established associations between EA, treatments, and neurologic outcomes. However, these studies have not adjusted for the treatment effects of anti-seizure medications (ASM). Not adjusting for treatment is problematic because several recent studies suggest aggressive ASM use, especially intravenous anesthetic drugs like *propofol*, may be harmful. However, aggressive treatment is reserved for more severely ill patients, thus these studies have been criticized for failing to adequately adjust for the type and severity of medical illness and epileptiform activity. Adjusting for these factors has been challenging because of the complex interactions and feedback loops involved. Yet, without adjusting for these factors, it remains unclear whether associations between EA and poor outcomes are due to over-treatment, underlying illness, or effects of EA.  **Added value of this study**  We study the harm caused by the different intensities of untreated EA as measured by the long-term degree of disability in critically ill patients. Major challenges with estimating such an effect are -- high-dimensional data with complex interactions between drugs and EA burden over time and low signal-to-noise ratio. We design a principled framework for estimation of causal effects using observational data that leverages pharmacokinetics and pharmacodynamics along with an interpretable matching approach to adjust for these confounders including drug response, medical history, and demographics. We apply our framework to estimate the effect of EA on neurologic outcomes. We find that high levels of EA over a brief period, when untreated, increase the chance of a poor outcome by 16.7%; and milder but long-lasting EA increases risk by 11.2%. Importantly, unlike currently popular black-box machine learning methods, our approach is designed for interpretability, allowing neurologists to verify the quality of our analyses via chart review.  **Implications of all the available evidence**  Our new approach allowed for the first time credible causal estimates of how much harm is caused by EA and in which types of patients. Our results not only confirm that EA burden (adjusted for anti-seizure medication effects) indeed worsens neurologic outcomes, but careful analysis illustrates that there exist important subgroups that are more affected. These results lay the foundation for developing an optimal treatment policy for EA burden to improve patient outcomes. |
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**Summary**

**Background** Many problems in neurology lead to similar analytical challenges: physicians cannot easily estimate the effects of interventions because the causal effects of illness and treatments are entangled. Performing studies is challenging: there are not enough patients for high-dimensional observational causal analysis, and randomized controlled trials often cannot ethically be conducted. However, mechanistic knowledge is available, for example about how drugs are absorbed, and this knowledge together with observational data could potentially suffice – if we knew how to combine them.

**Methods** We design a novel framework for estimating causal effects in high-stakes situations using observational data that has complex interactions between drugs and observations over time. Our framework uses mechanistic modeling as pharmacodynamics with an interpretable matching method to adjust for confounders. Our approach provides interpretable matched groups critical for troubleshooting such complex problems. Neurologists performed a chart review by analyzing the matched groups using the doctors’ notes that were not used for matching. Such chart review helped to argue about the quality of the matched groups and the existence of unobserved confounding.

**Findings** We find that high levels of epileptiform activity (75% EA burden), when untreated for a six-hour window, have, on average, a 16.7% increased chance of a poor outcome such as severe neurologic disability or death; and mild-but-long-lasting EA (average EA burden ≥ 50%) increases the risk of the poor outcome by 11.2%. We found significant heterogeneity in the size of the effect depending on pre-admission covariates. For instance, patients with central nervous system infection or toxic metabolic encephalopathy are affected by EA more than most other patients.

**Interpretation** Our findings have two primary implications for the treatment of EA: (1) Treatment should be based on EA duration as well as intensity. Intense periods of EA burden (max EA), even if relatively brief (6 hours) lead to worse outcomes. By contrast, sustained periods of EA (mean EA burden) show a binary relationship with the outcome: EA *<* 50% has minimal effect, but EA ≥ 50% causes a worse outcome. This suggests interventions should put a higher priority on patients with an average EA burden higher than 50%, while treatment intensity should be low and conservative when EA intensity is low. (2) Treatment policies should be based on admission profile, because the potential for EA to cause harm depends on age, past medical history, the reason for admission, and other characteristics. By contrast, current treatment protocols used in hospitals tend to be generic, recommending treatment be tailored based on the intensity or duration of EA but providing little guidance on how to take other patient characteristics into account.

**Funding** NIH R01NS107291.

**Introduction**

EA is common in critically ill patients, affecting more than half of patients who undergo electroencephalography (EEG) in critical care2–5. Prolonged EA is associated with in-hospital mortality, and survivors often suffer from long-term functional and cognitive disability6–9. However, despite a growing literature indicating EA is associated with poor outcomes10, there is debate about whether (a) EA is part of a causal pathway that worsens outcomes and thus requires aggressive treatment, or (b) worsened outcomes are due to mechanisms other than EA such as medication side-effects or the inciting illness, with EA as an epi-phenomenon11–16.

Studies of EA to date have suffered from a variety of limitations. First, a hypothetical clinical trial studying EA would need to randomly induce EA while limiting treatments, which is neither possible nor ethical. Second, sample sizes for observational EA datasets contain complex interactions with anti-seizure medications (ASM). Physicians administer ASMs based on patients’ EA, and in turn, EA is affected by ASMs. This creates entanglement (see Figure 1) between EA (treatment) and ASMs (confounder), obscuring the true causal effect of EAs. Further, the observational datasets are noisy, and there are potentially important variables that are not systematically recorded. Ignoring these complexities can lead to biased estimates of causal effects. Thus, a naïve statistical analysis is doomed to fail, and using black-box machine learning models in analysis or decision can lead to erroneous conclusions and potential harm.

Our approach to understanding the heterogeneous causal effects of EA - from high-dimensional patient data with complex time-series interactions - focuses on an interpretability-centered framework where a physician should be able to verify the quality of every single step in the analysis, from how a current patient compares to past patients (case-based reasoning), how drug absorption and response is modeled, and understand the relative importance of variables. We leverage domain knowledge captured by pharmacokinetic-pharmacodynamic (PK/PD) models to describe clinical-decision-physiological-response interactions, allowing us to identify individuals likely to react similarly to treatments. We learn a flexible distance metric on the space of covariates to perform high-quality matching for estimating both medium and long-term causal effects of clinical decisions and physiological responses, and the matched group constructed for each patient can be validated via chart review.

Using this framework, we perform the first causal analysis of a common form of potentially harmful electrical brain activity known as “epileptiform activity” (EA, also called “ictal-interictal-injury continuum activity”1).

Prior studies of EA have used regression models to adjust for medical history and demographic factors7–9,17 and interpreted the resulting regression coefficient for EA as the causal effect of EA on the outcome. While this approach is appealing for its simplicity, it is not appropriate to interpret regression coefficients as causal in the presence of strong confounding interactions. Conventional prognostic modeling approaches put one at risk for misinterpreting associations between high levels of ASM, EA, and poor outcomes as causal even if no causal link exists.

Our framework is different in that it tightly matches patients on relevant confounding factors. We adjust for important PK/PD parameters to better characterize individualized responses to anti-seizure medications; this mechanistic information helps compensate for our large but still limited sample size.

In a nutshell, the following are the *four* main contributions of our work: (1) a novel framework that combines mechanistic modeling with a powerful matching method to adjust for complex time-series confounders. (2) we provide the first (to our knowledge) estimate of the causal effect of EA on neurologic outcomes in patients with a critical illness. We find that a higher EA burden indeed leads to worse neurologic outcomes, in a way that depends on the intensity and duration of EA. (3) our results provide insights into individualized potential outcomes. For example, patients with central nervous system infection or toxic metabolic encephalopathy are affected by EA more than most other patients. (4) we leveraged the interpretability of our approach to validate our matched patients via chart review. The consensus in the chart review found that the matches were of high quality, matching patients with similar prognoses.

**Preliminaries**

*Cohort.* Our study is a retrospective cross-sectional analysis of patients admitted to Massachusetts General Hospital (MGH) between September 2011 - February 2017. Institutional review boards at MGH, Duke University, and University of North Carolina at Chapel Hill approved the retrospective analysis without requiring written informed consent. Inclusion criteria included age ≥18 years, and monitoring with continuous EEG for > 2 hours. Patients with poor quality of EEG signal for > 30% of the EEG were excluded. For patients with multiple hospitalizations, we only analyzed the first visit. The final cohort contained 995 critically ill patients.

For each patient we collected demographics (gender, marital status, and age), clinical factors (history of seizures or epilepsy, chronic kidney disease, etc.), and admission diagnosis (e.g. cancer, subarachnoid hemorrhage, etc.). These are referred to as the pre-admission variables. See Table 2.

*Outcomes Metric.* The neurologic outcome at hospital discharge is quantified on a 0 to 6 ordinal scale, the Modified Rankin Scale (mRS). Post-discharge outcome is frequently binarized into poor (mRS≥4) and favorable (mRS≤3) outcome9, as we do here.

*Complex Temporal Interactions*: *Drug treatments and EA.* Based on EEG findings, physicians adjust the types and dosage of ASMs. This observation-treatment cycle results in: (1) a time series of average EA burden over the past 6 hours and (2) a time-series of doses for 6 commonly used ASMs (Lacosamide, Levetiracetam, Midazolam, Phenobarbital, Propofol, and Valproate) received at time-step t. We chose 6 hours as a reasonable amount of time to observe the effects of ASMs on EA and for physicians to adjust ASM treatment. Details on how EA signals were identified are in Appendix C.

*Clinically Relevant Summaries of EA Burden Over Time.* We summarize the EA time series in two clinically relevant ways, referred to as EA burden:

1. Emean: Mean EA burden measures the average proportion of time a patient experiences EA in the first 24 hour recording period.

2. Emax: Max EA burden measures the 6 hour sliding window with the highest proportion of EA within the first 24 hour recording period.

By quantifying EA burden in these two ways, we seek to separately understand the harm caused both by brief intense EA and prolonged periods of less intense EA.

*Effects of EA Burden.* We aim to estimate how much untreated epileptiform activity (of different intensities) worsens neurological outcomes. Our estimand of interest is the probability of a poor outcome if the patient has EA burden (Emax or Emean) equal to a given level in the absence of treatment. We are interested in this “counterfactual outcome” (what would have happened without ASMs) because it disentangles the effects of EA from drugs on outcomes. For interpretability, we bin EA burden into 4 levels – mild (0% to 25%), moderate (25% to 50%), severe (50% to 75%), very severe (75% to 100%) (Appendix, Table 4). The choice of cutoffs was influenced by animal models suggesting an EA burden of 50% indicates when EA begins to damage the brain (Trinka et al., 2015). A sensitivity analysis of these choices is provided in Appendix D.

*Potential Confounders - Pre-admission Covariates and Drug-response Covariates.* In the ASM observation-treatment procedure, we observed two major sources of potential confounding. First, those with different diagnoses and characteristics may receive different ASM treatments, confounding the estimated harm caused by EA with the harm due to diagnosis or patient characteristics. To address this, a collection of 70 pre-admission covariates that could influence ASM treatment were selected by a group of practicing neurologists.

The second source of potential confounding comes from a patient’s drug response. Due to differing medical history, medical conditions, age, etc., patients respond differently to ASMs. This turn can affect the ASM treatment received and the final outcome. To account for this, we modeled each patient’s response to ASMs via one-compartment Pharmacokinetic/Pharmacodynamic (PK/PD) models. Further, we adjust for the confounding due to patients’ diagnosis, characteristics, and drug-responsiveness via a distance metric learning-based matching algorithm, Matching After Learning To Stretch (MALTS)19 which is an interpretable and accurately causal estimation method.

**Analysis Framework**

Our framework is shown in Figure 2. The first step is the identification of physiological phenomena that might affect long-term neurologic outcomes. These are frequently not recorded directly; relevant patterns must be extracted from raw waveforms. Examples include blood pressure and serial blood cultures in patients with sepsis; heart rhythms, oxygen levels, and blood electrolyte levels in patients with cardiac arrhythmias; urine output, body weight, and blood electrolytes in patients with acute kidney failure; or, as in this paper, detecting EA from EEG signals. Our framework estimates the long-term effects of these patterns. However, raw waveform data rarely exists in settings without clinical interventions: we must control for the effects of interventions, for example, in the scenarios mentioned above: blood pressure medications and antibiotics; medications to abort arrhythmias; electrolyte infusions, diuretic drugs, and hemodialysis; or ASM administered to reduce EA.

We combine demographics (e.g., age, weight) and patient characteristics within a PK/PD model to estimate drug response parameters for each patient. The patient data, including drug response parameters, are used for high-quality matching; each patient is matched almost exactly to patients with similar characteristics, medical history, and drug response parameters. Almost-exact matching18,19 matches patients directly on potential confounders (not on proxies like propensity scores). Matched groups permit case-based reasoning and allow estimating the effects of both EA and drugs on outcomes. In addition, domain experts can perform chart reviews for matched groups to evaluate matching quality.

**Results**

With the EA data summarized above, we used our framework to provide a causal analysis of the effect of EA on neurologic outcomes.

*Average Effect of Max EA Burden on Patient Outcomes.*

Figure 3(a) illustrates our first main result: those with higher levels of Emax are at higher risk of poor neurologic outcomes. Moreover, the risk of a poor outcome increases monotonically as EA burden increases, culminating in anaverage increase of 16.7% when a patient’s untreated EA burden increases from mild (0 to 0.25) to very severe (0.75 to 1).

*Average Effect of Mean EA Burden on Patient Outcomes.*

Figure 3(b) shows our other main result: those with higher Emean are also at higher risk of a poor outcome. Unlike Emax, the risk shows a step increase above even a moderate EA burden, [0*.*25*,*0*.*50). Our results indicate that severe and very severe prolonged EA burden (over 24 hours) increases the risk of the poor outcome by 11.2% compared to mild prolonged EA burden.

*Heterogeneity in Effects for Max EA Burden.*

We found significant heterogeneity in the effect size depending on pre-admission covariates. We quantify the relative change in outcome from a very severe Emax as the ratio of the difference of expected potential outcomes under high and low EA burden and the expected potential outcome under low EA burden. Based on this relative effect, patients with central nervous system (CNS) infections or toxic metabolic encephalopathy are at higher risk of a worse outcome in response to a large Emax. We conjecture this may be the result of CNS infection and EA leading to a higher inflammatory response, exacerbating the neurologic injury. Figure 4(a) breaks down the population into subpopulations with differing conditional average treatment effects.

We examined race and gender as possible effect modifiers of EA burden. Figure 4(b) shows race does not modify the risk from Emax. By contrast, sex does modify the risk: poor outcome probability is more affected by very severe Emax in males (see Figure 4(c)).

**Interpretable Matched Group Analysis**

Here, we assess the quality of the matched groups. These analyses determine trust of the causal conclusions.

*Stretch Coefficients Give Insight into the Matching Process.* Visualizing stretch coefficients provides insight into the relative importance of variables used in matching. For Emax (Figure 5), two measures of illness severity were heavily weighted (iGCS and APACHE II). Age and systolic blood pressure were the second and fourth most important variables. These observatiothe ns suggest that our matched groups essentially consist of individuals that agree on factors representing overall health and current level of neurologic impairment. In Figure 5, one can also see that the three least important matching variables are Hill coefficients and *ED*50 parameters from one of the anti-seizure medications. This stands in contrast with *ED*50 for Propofol, one of the top five *most* important variables. This suggest that information about responsiveness to Propofol, a potent intravenous anesthetic drug used to treat seizures, is much more critical in estimating causal effects of EA on outcome than other less potent ASMs.

*Matched Groups are Validated by Neurologist Chart Review*

To ensure validity of our causal conclusions, it is crucial that the matching process does not overlook major unobserved confounding factors. Inspired by similar approaches in the social sciences20, one can check for unobserved confounders by having a domain expert perform a post-facto analysis of matched groups. This approach is well suited for medical data, because in addition to factors that are easy to quantify, it is common for a patient to have a large volume of qualitative information in the form of doctor’s notes and documentation. This allows us to check for both qualitative and quantitative sources of potential unobserved confounding.

For our matched groups analysis, three neurologists, Chart Reviewers 1, 2, and 3 (CR 1-3), were sent 3 randomly chosen matched groups for manual chart review. Reviewers were asked to independently make a qualitative analysis of the matched groups and report their outcome prognosis (chance of a poor outcome) and likelihood of experiencing a high EA burden.

As shown in Table 1, the neurologists found no problematic sources of confounding. Moreover, we can observe which factors each group was matched tightly on. For example, group 3 is tightly matched with patients having similar APACHE II scores and all but one having relatively good prognoses. By contrast, group one is 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 which factors have been properly controlled for, such as age, and which factors are either unimportant or lack the sample size to tightly match upon, such as many of the less common medical conditions.

**Discussion**

We presented four main contributions in this work: (1) First, a novel framework that combines mechanistic modeling with a powerful matching method to adjust for complex timeseries confounders. (2) Second, the first (to our knowledge) estimate of the causal effect of epileptiform activity (EA) on neurologic outcomes in patients with critical illness. We find that higher EA burden indeed leads to worse neurologic outcomes (Figure 3), in a way that depends on the intensity and duration of EA. (3) Third, our results provide insights into individualized potential outcomes. For example, patients with central nervous system infection or toxic metabolic encephalopathy are affected by EA more than most other patients. (4) Finally, we leveraged the interpretability of our approach to validate our matched patients via chart review. The consensus in the chart review found that the matches were of high quality, matching patients with similar prognoses.

*Clinical Implications.* Our findings have two primary implications for treatment of EA: (1) Treatment should be based on EA duration as well as intensity. Intense periods of EA burden (max EA), even if relatively brief (6 hours) lead to worse outcomes. By contrast, sustained periods of EA (mean EA burden) show a binary relationship with outcome: EA *<* 50% has minimal effect, but EA ≥ 50% causes worse outcome. This suggests interventions should put higher priority on patients with mean EA burden higher than 50%, while treatment intensity should be low and conservative when EA intensity is low. (2) Treatment policies should be based on admission profile, because the potential for EA to cause harm depends on age, past medical history, reason for admission, and other characteristics. By contrast, current treatment protocols used in hospitals tend to be generic, recommending treatment be tailored based on the intensity or duration of EA but providing little guidance on how to take other patient characteristics into account. As a result, treatment approaches vary widely between doctors.

*Results in context.* Our work builds on prior results demonstrating associations between EA, treatments, and neurologic outcomes. Oddo et al10 studied 201 ICU patients where 60% had sepsis as an admission diagnosis. They found that EA (seizures and periodic discharges) were 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 ASM, including phenytoin (given to 67% of patients), levetiracetam (62% of patients), lorazepam (57% of patients), and four other drugs. Tabaeizadeh et al.21 found that the maximum daily burden of EA/seizures is associated with higher risk of poor outcome in 143 patients with acute ischemic stroke. However, they did not control for ASMs which were given to 83% of patients. Lack of adjusting for drug use is also found in the pediatric literature on EA6. Not adjusting for treatment is problematic because a growing number of studies suggest aggressive ASM use, especially with intravenous anesthetic drugs like propofol, may be harmful. For example, a recent retrospective study of 467 patients with incident status epilepticus of Marchi et al.22 found that therapeutic coma was associated with poorer outcome, higher prevalence of infection, and longer hospital stay23,24. 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. Adequately adjusting for these factors has been challenging before now because of the complex interactions and feedback loops involved. However, without adjusting for these factors, it remains unclear whether the association between EA and poor outcomes is due to over-treatment, the underlying illness, or the direct effects of EA. Without answering this question, it remains unclear whether current treatment approaches are helping or hurting patients.

We addressed this gap by introducing an analytic approach that simultaneously accounts for the entwined and time-varying effects drug and EA burden, and their interactions with patient characteristics. A key component of our approach is adjusting for patients’ PK/PD parameters to account for patient heterogeneity. Critically ill patients can be different in many ways including measured and unmeasured variables. By accounting for PK/PD parameters, we were able to adjust for exposure to anti-seizure drugs, such as phenytoin and pentobarbital, where the medications themselves may worsen outcomes. Another key innovation is our application of an advanced methodology designed specifically for causal inference using observational data. In the studies cited above, multivariate regression was used to adjust for potential confounders. The nature of observational data and multivariate regression (model misspecification) have made it impossible to establish a causal link between EA and outcomes. The matching approach in MALTS, being a causal inference method, achieves both the flexibility of being free of model misspecification (non-parametric) and the interpretability of the learned weights, creating less biased estimates of the causal effects. With this new approach, we are able to provide for the first time credible estimates of how much harm EA causes and in which types of patients.

Our approach has several limitations that could be improved in future work. When evaluating the EA burden, it would be worthwhile in future work to consider the subtype of EA (GPD/LPD/LRDA), discharge frequency for periodic discharges, and the spatial extent of EAs. We currently do not have high quality human labels at the necessary resolution, but this is in development. On the other hand, the automatic EA annotator, based on a deep neural network, although not perfect, achieves similar inter-rater reliability to experts for EA detection25. The PK/PD model can be further improved by including more mechanistic or physiological detail, such as a context sensitive half-life for propofol26.

In summary, our results present a data-driven causal statistical inference approach to quantify the harm caused by EA. We not only confirm that EA burden (adjusted for ASM) indeed worsen neurologic outcomes, but careful analysis illustrates that there exist important subgroups that are more affected. Based on this, a future direction is to learn an interpretable optimal treatment policy for EA burden to improve patient outcomes.

**Contributors**

HP, KH, HS, AV, CR, MBW conceptualized the study. WG, JJ, SZ, MBW curated the data.

WG and JJ developed the neural network model for detecting EA in raw EEG data. HP, KH, HS analysed the data. MBW and JS acquired funding. HP, KH, HS, AV, CR, MBW created the methodology. AV, CR, MBW gave supervision. AS, SZ, MBW performed chart review on the matched groups. XX verified the data. HP, KH, HS, created the figures. HP, KH, HS, AV, CR, MBW wrote the original draft. All authors reviewed and edited the final manuscript. HS, SZ, AV, CR, MBW had access to raw data and 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. All other co-authors report 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 participant data is made available.

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