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Effect of Epileptiform Abnormality Burden on Neurologic Outcome and Anticonvulsant Drug Management After Subarachnoid Hemorrhage

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Abstract

Objective: To quantify the burden of epileptiform abnormalities (EAs) including seizures, periodic and rhythmic activity, and sporadic discharges in patients with aneurysmal subarachnoid hemorrhage (aSAH), and assess the effect of EA burden and treatment on outcomes.

Methods: Retrospective analysis of 136 high-grade aSAH patients. EAs were defined using the American Clinical Neurophysiology Society nomenclature. Burden was defined as prevalence of <1%, 1–9%, 10–49%, 50–89%, and >90% for each 18–24 hour epoch. Our outcome measure was 3-month Glasgow Outcome Score.

Results: 47.8% patients had EAs. After adjusting for clinical covariates EA burden on first day of recording and maximum daily burden were associated with worse outcomes. Patients with higher EA burden were more likely to be treated with anti-epileptic drugs (AEDs) beyond the standard prophylactic protocol. There was no difference in outcomes between patients continued on AEDs beyond standard prophylaxis compared to those who were not.

Conclusions: Higher burden of EAs in aSAH independently predicts worse outcome. Although nearly half of these patients received treatment, our data suggest current AED management practices may not influence outcome.

Keywords

continuous EEG; epileptiform abnormalities; periodic discharges; neurologic outcomes; subarachnoid hemorrhage

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1. Introduction

Epileptiform abnormalities (EAs) including seizures, periodic and rhythmic patterns, and sporadic discharges are seen in electroencephalogram (EEG) recordings in up to 20% percent of patients with aneurysmal subarachnoid hemorrhage (aSAH) (Claassen *et al.*, 2006). The presence of periodic discharges and seizures has been linked to worse functional and cognitive outcomes (Claassen *et al.*, 2006; De Marchis *et al.,* 2016). Nevertheless, there is limited and conflicting data on how the burden and subtype of EAs influence outcome in patients with aSAH (Crepeau *et al.*, 2013).

With the publication of consensus recommendations and increased application of continuous electroencephalogram (cEEG) monitoring in critically ill patients, the diagnosis of seizures and other EAs is increasing (Sutter *et* al., 2011; Claassen *et al.*, 2013; Ney *et al.*, 2013). In a large series of critically ill mechanically ventilated patients in the US, use of cEEG increased by 33% per year on average, and the number of hospitals using cEEG doubled between 2005 and 2009 (Ney *et al.*, 2013). Anti-epileptic drugs (AEDs) are frequently prescribed not only for seizures but also for other EAs, despite absence of data on clinical response to treatment or effect of treatment on short and long-term neurologic outcomes (Sivaraju, Gilmore 2016).

The primary objective of our study is to investigate the dose-response relationship between epileptiform abnormalities and outcomes in patients with aneurysmal subarachnoid hemorrhage. Our secondary objective is to define AED prescription practices, and assess whether our data provide evidence that treatment improves outcomes.

2. Materials and Methods

2.1 Study Design

This is a retrospective cohort study of patients from the MGH aneurysmal subarachnoid hemorrhage (aSAH) database admitted between September 2011 and February 2016. The study was conducted under a protocol approved by the Institutional Review Board. Informed consent was not required for this retrospective study. The aSAH database includes patients with high grade aSAH (≥Hunt and Hess 3 and ≥Fisher 3) or who undergo continuous EEG or multimodality monitoring. All patients with age >18 years, an identified aneurysm, and continuous EEG monitoring for >18 hours were included. We excluded non-aneurysmal SAH, including SAH caused by trauma or other vascular malformations. Presence of aneurysms was confirmed by computed tomography and conventional angiography.

2.2 Clinical covariates

Demographic and clinical variables were abstracted from the electronic health record. Clinical covariates included the Hunt and Hess (HH) and Fisher scores, admission Acute Physiology and Chronic Health Evaluation II (APACHE II) score, aneurysm treatment modality, occurrence of re-bleed, treatment with AEDs, use and duration of mechanical ventilation and duration of ICU stay. Per institutional protocol, AED prophylaxis was continued until the aneurysm was secured or for 7 days post craniotomy. Unless contraindicated, levetiracetam was the prophylactic AED of choice. Patients were coded as

having been treated with AEDs if they were continued for longer than the protocol standard. In addition, we recorded time points at which AED doses were either escalated or decreased. Primary indications for AED continuation were: clinical seizures, and/or scalp or depth seizures, periodic and rhythmic patterns or sporadic discharges, at the treating physicians discretion. Additional or alternate AEDs, frequently phenytoin and lacosamide, were used for refractory seizures or other persistent EAs at the treating physician's discretion. Routine prophylactic dose for levetiracetam was 500mg BID. If treatment was escalated, standard levetiracetam dose ranged from 750 mg BID to a maximum of 2000mg BID. The typical loading dose for phenytoin was 20mg/kg, and maintenance dose was titrated to a phenytoin level of 10–20 ug/ml. If given as a load, the typical loading dose for lacosamide was 400mg, and maintenance dose was 100 to 200mg BID.

Delayed complications that we studied included delayed cerebral ischemia (DCI) and hospital acquired infections (HAI), including hospital acquired pneumonia (HAP). Two neurologists independently determined whether each patient developed DCI, defined using published consensus guidelines (Vergouwen *et al.*, 2010). Inter-rater agreement of independent review was excellent (95.83%) for overall agreement on the presence or absence of any delayed ischemic events (Zafar *et al.*, 2016). Any disagreements were further adjudicated following a published protocol (Zafar *et al.*, 2016). HAIs were confirmed by positive cultures or radiographic and clinical evidence of a respiratory tract infection.

2.3 cEEG protocol and EEG features

The institutional protocol recommends 10 days of cEEG monitoring for ischemia detection in high grade (≥HH3F3) patients. Additionally, patients with suspected subclinical seizures underwent cEEG monitoring for variable duration as indicated. All cEEG recordings were obtained using 21 electrodes and the conventional International 10–20 system. Raw EEG data was reviewed and reported by 2 clinical neurophysiologists per institutional protocol. EEG reports were updated at least twice daily. A board certified neurologist and clinical neurophysiologist (SFZ) with certification in the American Clinical Neurophysiology Society EEG terminology exam administered by the Critical Care EEG Monitoring Research Consortium (Hirsch *et al.*, 2013) reviewed all the EEG reports for abstraction and independently reviewed raw cEEG data to confirm appropriate designation of EAs. This reviewer was blinded to outcomes at the time of EEG review.

Epileptiform abnormalities (EAs) were defined as seizures, periodic and rhythmic patterns and sporadic discharges. Periodic and rhythmic patterns, and sporadic discharges were defined using the American Clinical Neurophysiology Society (ACNS) nomenclature (Hirsch *et al.*, 2013). The ACNS recognizes the following EEG patterns: lateralized periodic discharges (LPDs), bilateral independent periodic discharges (BIPDs), generalized periodic discharges (GPDs), lateralized rhythmic delta activity (LRDA), generalized rhythmic delta activity (GRDA), and sporadic discharges. Electrographic seizures were defined as spikes, sharp waves, sharp-slow wave complexes, or rhythmic activity lasting at least 10 seconds at a frequency of 3Hz or more, or patterns with lower frequencies with evolution in frequency, morphology, or location (De Marchis *et al.,* 2016).

2.4 EA Burden: per epoch, and overall exposure

Burden of EAs in any single 18–24 hour epoch was quantified based on the fraction of time during the epoch occupied by the pattern, using ACNS terminology: *rare*: <1%, *occasional*: 1–9%, *frequent*: 10–49%, *abundant*: 50–89%, *continuous*: ≥90% (Hirsch *et al.*, 2013). For each 18–24 hour epoch of recording, we recorded EA pattern types and burden.

The overall EA exposure or burden over the entire course of cEEG monitoring does not have a standardized definition. We therefore examined three alternative formulations as quantitative markers of the overall EA burden for each patient:

1) *Presence:* presence of any EAs within any epoch;

2) *First day burden*: burden within the *first* 18–24 hour epoch;

3) *Maximum daily burden*: maximum EA burden within *any* 18–24 hour epoch.

As GRDA is a more benign pattern, with minimal association with both seizures and DCI (Kim *et al.*, 2017; Ruiz *et al.*, 2017; Struck *et al.*, 2017), we excluded isolated GRDA, including isolated GRDA with plus features when evaluating EA burden calculations. We also excluded isolated GRDA with plus features as it has a lower association with seizures (Ruiz *et al.*, 2017).

2.5 Outcomes

Our primary objective was to assess the impact of EA burden on outcomes. Our outcome measure was the 3-month Glasgow Outcome Scale (GOS); GOS 1: death; GOS 2: vegetative state; GOS 3: severe disability; GOS 4: moderate disability; GOS 5: good recovery (Jennett, Bond 1975). GOS was abstracted from physician and physical therapy clinical examinations within 3 months of discharge following an established protocol described in prior work (Zafar *et al.*, 2017). For analysis we dichotomized outcomes into poor (GOS 1–3) vs. good (GOS 4–5).

2.6 Statistical analysis

Median and inter quartile ranges were calculated for descriptive analysis. We dichotomized outcomes as poor (GOS 1–3) vs good (GOS 4–5). In the text, values are reported in the format: median [IQR].

Univariate analysis was performed using Fisher's exact test for dichotomized and categorical variables, and the Mann-Whitney-U-test for continuous variables. Significance was set at 0.05, and 2-sided P values are reported. Multivariate analysis was performed using a logistic regression model to assess the association (odds ratios) between EA burden and poor outcome, and to adjust for other covariates believed to contribute to poor outcomes (Witsch *et* al., 2016; Zafar *et al.*, 2017). Odds ratios are presented with 95% confidence intervals as OR [95%CI]. The goodness of fit for the logistic regression models was assessed using the Hosmer-Lemeshow test.

3. Results

136 patients met inclusion criteria. The main clinical and demographic characteristics of the cohort are summarized in Table 1. The median age of our cohort was 57 years. 70.6% (n=96) of patients were female. 47.8% (n=65) had EAs (excluding GRDA). Hereafter, any reference to "EAs" excludes isolated GRDA.

Patients with EAs were older (62 [51–74] vs 54.5 [45–65] years, p=0.003), and were more likely to have higher HH scores (47.7% with HH 4–5 vs 29.5 %, p=0.035) and higher APACHEII scores (18 [11.5–18.5] vs 11 [6–18] p= <0.0001). Patients with EAs were also more likely to suffer hospital-acquired pneumonia (HAP) (52.3% vs 31% p=0.015). DCI was significantly more common in patients with EA (65.1%) vs. those without (35.2%, p=0.001). This finding was also demonstrated in our prior work showing that the emergence of periodic discharges, epileptiform activity and lateralized rhythmic delta activity predict DCI (Kim *et al.*, 2017).

Table 2 shows the frequency and distribution of EEG patterns in our patient cohort. Sporadic epileptiform discharges (47.8%, n=65) were the most frequent. 18.4% (n=25) patients had isolated GRDA. Only 4.4% (n=6) patients had electrographic seizures. Among patients with EAs, most had a maximum daily burden of 10–49%/frequent (21.5%, n=14) and 50–89%/abundant (24.6%, n=16). Interestingly almost half (41.5%, n=27) the patients did not have any EAs in the first epoch, and developed EAs as further EEG recording was obtained.

3.1 EA burden and outcomes: Univariate analysis

Three month outcomes were obtainable for 114 patients. Figure 1A shows overall EEG findings, including EA type and burden over days, comparing patients with good vs. poor outcomes. The figure highlights the day-to-day variations in EA burden and summarizes the cumulative EA burden over days. Many of the patients did not develop EAs until after 24–48 hours of recording. Patients with higher burden of EAs were more likely to have worse outcomes.

Associations of EAs and outcome on univariate analysis are shown in Figure 2. Presence of EAs was associated with worse 3-month outcomes (GOS 1–3) (OR 3.0[1.4–6.3], p =0.006). Among patients with EAs, higher first day burden was significantly associated with worse outcomes (<50% vs. ≥ 50%, OR 6.7 [1.2–38.2], p=0.03). Higher maximum daily burden was also associated with worse outcomes (<50% vs. ≥ 50%, OR 3.8 [1.2–12.1], p=0.03).

3.2 EA burden and outcomes: Multivariate analysis

We created multivariate logistic regression models for: EA presence, first day burden (<10% vs. >10%, <50% vs. >50%), and maximum daily burden (<10% vs. >10%, <50% vs. >50%). On multivariate analysis, after adjusting for age, gender, HH score, APACHE II score, DCI, HAP, re-bleeding and use of AEDs, although presence of EAs was associated with worse 3-month outcome, this relation was no longer significant (OR: 2.2, [0.9–5.8], p=0.086). After adjusting for covariates, a higher first day burden (<10% vs. ≥10% and <50% vs. ≥ 50%) was significantly associated with worse outcomes (OR 4.1 [1.1 – 14.7] and OR: 6.6 [1.3 −34.5] respectively). Similarly, after adjusting for co-variates, a higher maximum daily

burden (<10% vs. ≥10%, and <50% vs. ≥ 50%) continued to be significantly associated with worse outcomes (OR 4.5 [1.6 – 12.7] and OR 5.3 [1.5 −18.3], respectively) (Table 3).

Using a multivariate logistic regression model we also assessed the probability of worse outcomes (GOS 1–3) with increasing EA burden (none, rare, occasional, frequent, abundant, continuous). After adjusting for covariates we found that both higher first day burden (OR 1.5 [1.1– 2.1] p:0.012) and higher maximum daily burden (OR 1.5 [1.2–2.0] p:0.008) were associated with a higher probability of worse 3-month outcomes (Figure 3A and3B). Figure 3A and3B also show the observed proportions of poor outcome for each burden subgroup. Although some variability is evident in the observed proportions, overall there is a clear monotonically increasing dose-response relationship, with mortality increasing as a function of EA burden, as suggested by the multivariate model.

3.3 AED prescription and outcomes

In addition to EA burden and outcomes, we examined associations between EA burden, AED treatment practices, and outcomes. Patients with EAs were more likely to be continued on AEDs beyond the protocol standard, (70.8% vs. 43.7%, p=0.002, Table 1). Patients with EAs were also significantly more likely to be discharged on AEDs (p=0.003) (Table 1).

As detailed in section 2.2, reasons for AED continuation included clinical seizures, and/or scalp or depth seizures, periodic and rhythmic patterns or sporadic discharges, at the treating physicians discretion. We also assessed additional AED escalation specifically for EAs as a treatment indication. In figure 1B we show a detailed examination of AED continuation beyond standard prophylaxis. EEG findings over days for all 136 patients are shown, comparing patients that received continued AED treatment versus those who did not receive any AED after standard prophylaxis was completed. In addition, we highlight patients that received further AED treatment and escalation (dose increase or addition of alternate AEDs) specifically in response to scalp EAs. Patients with maximum burden >50% were more likely to have AED escalation for EAs compared to those who had maximum burden <50% (OR: 3.1, CI: 1.3–7.6, P=0.0144).

With respect to outcomes, there was no significant difference in outcomes between patients with EAs continued on AEDs compared to those who were not (OR: 1.6 [0.5 – 4.5], p=1.00). Even after adjusting for EA burden, age, gender, illness severity and other known predictors of outcome (including HH, APACHE II, DCI, HAP) (Witsch *et* al., 2016; Zafar *et al.*, 2017), there was no significant difference in outcomes between patients with EAs treated with AEDs compared to those who were not (OR 0.9 [0.2–3.3], p=0.899).

4. Discussion

Our data suggest that the burden of EAs exerts a dose-dependent negative impact on 3-month neurologic outcome after subarachnoid hemorrhage. Previous work has already established that prolonged exposure to *electrographic and clinical seizures*, produces worse outcomes in patients with aSAH (De Marchis *et al.*, 2016) and other conditions (Payne *et al.*, 2014). Our results now expand this finding to include less severe forms of pathological brain activity, namely sporadic discharges and the seizure like rhythmic and periodic EEG patterns

that have come to be called *ictal interictal continuum (IIC) patterns*. EAs when grouped together as simply “present” vs “absent” were not significantly associated with worse outcomes. However, the maximum daily burden and first day burden were independently associated with worse outcomes after adjusting for clinical covariates. Although patients in our cohort with EAs and particularly those with higher burden were more likely to receive prolonged and escalating doses of AEDs, we found no significant difference in outcomes between patients who were treated vs. those who were not. Thus, the optimal management approach remains uncertain.

In the Columbia Subarachnoid Hemorrhage Outcomes Project (SHOP), seizure burden was shown to be associated with worse outcomes (De Marchis *et al.*, 2016). 12% of patients undergoing continuous EEG monitoring were found to have seizures, and each hour of seizures was associated with worse functional and cognitive outcomes at 3 months (De Marchis *et al.*, 2016). Seizure burden was similarly associated with worse outcomes in a prospective study of critically-ill children (Payne *et al.*, 2014). The authors found that a seizure burden threshold of 20% per hour (12 min) was associated with neurologic decline after adjusting for diagnosis and illness severity (Payne *et al.*, 2014).

While patients with presence of periodic patterns in the SHOP cohort were found to have worse outcomes (Claassen *et al.*, 2006), the authors only adjusted for age, HH score and imaging findings. Another study found that the maximum persistence of periodic and rhythmic patterns during any 24-hour period was not associated with discharge outcomes in patients with aSAH (Crepeau *et al.*, 2013). However the study was underpowered (sample size of 68), and did not evaluate post-discharge outcomes or perform detailed analysis of periodic vs. rhythmic patterns (Crepeau *et al.*, 2013). Our study goes beyond these existing studies as we performed a more detailed analysis of EEG patterns using the ACNS criteria and a more robust analysis adjusting for additional known predictors of outcome (Witsch *et* al., 2016; Zafar *et al.*, 2017).

The overall prevalence of any periodic patterns in our cohort (25.0 %) was similar to that reported in the literature, with reports of periodic patterns seen in up to 20% of aSAH patients (Claassen *et al.*, 2006; De Marchis *et al.*, 2016). Few studies have looked at the prevalence of rhythmic delta activity in these patients, and have either been without application of the ACNS terminology (Claassen *et al.*, 2006) or without distinction between lateralized and generalized rhythmic delta activity (Crepeau *et al.*, 2013). Interestingly, however, we had a low prevalence of electrographic seizures (4.4%). This may also have been the result of stricter adherence to the ACNS terminology. Second, aggressive treatment of periodic and rhythmic patterns, and sporadic discharges may have prevented definite electrographic seizures on EEG. Regardless, this highlights the importance of using standardized terminology to avoid heterogeneity in EEG descriptions, and to allow comparisons across studies. Most studies on EEG patterns in critically-ill patients were done prior to the publication of the ACNS standardized nomenclature (Claassen *et al.*, 2006; Oddo *et al.*, 2009; Kurtz *et al.*, 2014), resulting in variation in the description of patterns.

Evidence is accumulating that periodic patterns may result in secondary brain injury (Sivaraju, Gilmore 2016), which may explain worse outcomes in patients with these

patterns. PET studies have shown that periodic patterns are associated with increased focal cerebral metabolism, similar to seizures (Struck *et al.*, 2016). A recent study investigating the association between periodic discharges on depth recordings and brain tissue oxygenation found that high frequency periodic discharges (≥ 2.0 Hz) were associated with brain tissue oxygenation (PbtO2) reduction, increased cerebral blood flow, and increased cerebral perfusion pressure (Witsch *et al.*, 2017). A similar study in patients with traumatic brain injury found that seizures and periodic discharges in depth recordings were associated with metabolic crisis as evidence by low brain glucose and elevated microdialysis lactate/pyruvate ratios (Vespa *et al.*, 2016). We hypothesize that the higher probability of worse outcomes in patients with high EA burden in our cohort may be secondary to a similar process of increased metabolic demand in the injured brain. With increasing EA burden increased blood flow may not match metabolic demand and this may result in secondary brain injury (Witsch *et al.*, 2017).

We also found that older patients were more likely to have EAs. Our observation expands previous reports that older patients are also more likely to have seizures, based on the SHOP cohort (De Marchis *et al.*, 2016). Neuro-degenerative changes from aging may result in a predisposition to seizures and other EAs, with aSAH unmasking or lowering the seizure threshold. Older patients are also more likely to have additional medical comorbidities (Creditor 1993), which may result in acute brain dysfunction, further lowering their threshold for EAs.

In addition to age, we found that patients who are sicker, with higher HH and APACHE II scores, and patients with hospital acquired pneumonia, were more likely to have EAs. Patients who developed DCI were also more likely to have EAs. This raises the long-debated question of whether underlying illness severity is the main driver of long-term outcomes and that EAs themselves are an epiphenomenon (Kaplan 1995). However, we found that even after adjusting for these covariates, higher EA burden remained associated with worse outcomes, supporting the hypothesis that it contributes to some degree of secondary brain injury.

cEEG can be used as a tool for ischemia detection in patients with aSAH (Foreman, Claassen 2012), and our findings suggest increased utility also as a prognostication tool, particularly in patients that are sicker and develop additional hospital-acquired comorbidities. Our study also underscores the performance of prolonged cEEG monitoring in patients with aSAH, particularly in sick, high-grade patients with early evidence of EAs, to assess the overall burden and stratify treatment based on burden and pattern subtype.

If increased EA burden does contribute to brain injury, more aggressive treatment might be warranted. Alternatively, even if effective, benefits of aggressive treatment might be offset by iatrogenic risks. While this question probably cannot be definitively addressed retrospectively, variation in management might provide a “natural experiment” that allows us to begin to understand this risk-benefit calculus. We found that AEDs were continued beyond the protocol standard in 56.7% of our patients. Patients with EAs were more likely to be discharged on AEDs. However, we found no difference in outcomes among patients with EAs that received AEDs beyond protocol standard vs. those that were not treated

beyond standard prophylaxis. There are several hypotheses that might explain this surprising finding. First, as evidenced by Figure 1, there is day-to-day fluctuation in EA burden even in the absence of AED treatment and escalation, with resolution of EAs in patients who were not continued on AEDs. This suggests some of these EAs may be self-limited and may not benefit from AED treatment. Second, patients with EAs were sicker, with higher APACHE II scores and higher likelihood of having metabolic derangements and infections. It is possible that the efficacy of AEDs is compromised by the impact of the medical comorbidities on brain function. Third, given EAs are frequently seen in patients with acute structural brain injury, with associated cytotoxic edema, excitotoxicity and breakdown of blood brain barrier, standard AEDs in isolation may not be efficacious, and a combination of AEDs, neurosteroids and N-methyl-D-aspartate (NMDA) receptor antagonists could be investigated in future studies (Zeiler *et al.*, 2014; Holtkamp 2018).

It remains possible that a beneficial effect from AEDs was not found due to an insufficient cohort size and/or small treatment effect. Thus a final possible explanation for not finding a significant difference is the variation in treatment practices as highlighted by our study. More than half of our patients with EAs received prolonged treatment, while the rest only received standard prophylaxis. Patients with higher burden and periodic patterns were more likely to be treated. In the absence of high quality evidence-based guidelines, such variations in AED treatment practices are common among physicians across institutions (Alvarez *et al.*, 2017). A multicenter study found that although use of cEEG is similar across institutions, there was substantial variability in the use of AEDs (Alvarez *et al.*, 2017). This variability in treatment of EAs likely stems from absence of treatment guidelines and absence of data on impact of treatment on outcomes. As a result, AEDs are frequently started for cEEG findings and often continued long-term (Kilbride *et al.*, 2009).

AEDs themselves are not benign, with up to 80 percent of patients experiencing side effects including cognitive slowing, gait instability and mood symptoms that can worsen quality of life (Brodie *et al.*, 1995; Baker et al., 1997; Perucca *et al.*, 2009). Prophylactic phenytoin use has been linked to worse outcomes in patients with neurological injury (Naidech *et al.*, 2005; Yoon *et al.*, 2015). Although levetiracetam appears to have better tolerability prospective studies are needed to evaluate the long-term impact (Szaflarski *et al.*, 2010, Pearl *et al.*, 2013). Whether standardized AED treatment protocols in patients with EAs can lead to better outcomes remains to be determined.

An important limitation of our study is its retrospective nature. In addition, most of our patients had high-grade aSAH limiting the generalizability of our findings to all aSAH patients and all ICU patients. Finally, the heterogeneity in AED treatment practices and dosing limits our ability to draw definitive conclusions regarding the impact of treatment on outcomes.

5. Conclusion

In conclusion, going beyond previous studies that show a higher burden of high frequency periodic discharges and lateralized rhythmic delta activity are associated with seizures, we find that these patients are also more likely to have worse outcomes (Ruiz *et al.*, 2017). Yet

we find no evidence of a clear benefit of broad unstandardized AED treatment. With the mounting evidence that EAs cause secondary brain injury and worsen outcomes, and the continuing uncertainty regarding how to intervene, the time is ripe to move toward interventional studies. Future multi-center randomized controlled studies to directly assess the impact of AED treatment need to be conducted, focusing specifically on these subgroups of patients, and using standardized ACNS nomenclature, in order to create evidence-based treatment protocols that may improve outcomes. Utilizing ancillary data such as PET scans and multi-modal monitoring including brain tissue oxygenation or microdialysis may help further stratify patients with EAs that have secondary brain injury, identifying those that would benefit most from AED management, and providing an opportunity for goal directed treatment.

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Abbreviations

AED	anti-epileptic drugs
ACNS	American Clinical Neurophysiology Society
APACHE II	Acute Physiology and Chronic Health Evaluation II
aSAH	aneurysmal subarachnoid hemorrhage
BID	bis in die
BIPDs	bilateral independent periodic discharges
cEEG	continuous electroencephalogram
DCI	delayed cerebral ischemia
EAs	Epileptiform abnormalities
EEG	electroencephalogram
GOS	Glasgow Outcome Score
GRDA	generalized rhythmic delta activity
GPDs	generalized periodic discharges
HAI	hospital acquired infection
HAP	hospital acquired pneumonia
HH	Hunt and Hess
IIC	ictal-interictal continuum

LPDs	lateralized periodic discharges
LRDA	lateralized rhythmic delta activity
NMDA	N-methyl-D-aspartate
SHOP	Subarachnoid Hemorrhage Outcomes Project

References

Alvarez V, Ruiz AA, LaRoche S, Hirsch LJ, Parres C, Voinescu PE, et al. The use and yield of continuous EEG in critically ill patients: A comparative study of three centers. Clin Neurophysiol 2017; 128: 570–8. [PubMed: 28231475]

Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia 1997; 38: 353–362 [PubMed: 9070599]

Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet 1995; 345: 476–479 [PubMed: 7710545]

Claassen J, Hirsch LJ, Frontera JA, Fernandez A, Schmidt M, Kapinos G, et al. Prognostic significance of continuous EEG monitoring in patients with poor-grade subarachnoid hemorrhage. Neurocrit Care 2006; 4: 103–12. [PubMed: 16627897]

Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med 2013; 39: 1337–51. [PubMed: 23653183]

Creditor MC. Hazards of hospitalization of the elderly. Ann Intern Med 1993; 118: 219–23. [PubMed: 8417639]

Crepeau AZ, Kerrigan JF, Gerber P, Parikh G, Jahnke H, Nakaji P, et al. Rhythmical and periodic EEG patterns do not predict short-term outcome in critically ill patients with subarachnoid hemorrhage. J Clin Neurophysiol 2013; 30: 247–54. [PubMed: 23733088]

De Marchis GM, Pugin D, Meyers E, Velasquez A, Suwatcharangkoon S, Park S, et al. Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome. Neurology 2016; 86: 253–60. [PubMed: 26701381]

Foreman B, Claassen J. Quantitative EEG for the detection of brain ischemia. Crit Care 2012; 16:216. [PubMed: 22429809]

Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013; 30: 1–27. [PubMed: 23377439]

Holtkamp M Pharmacotherapy for Refractory and Super-Refractory Status Epilepticus in Adults. Drugs 2018; 1–20. [PubMed: 29139091]

Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. Lancet 1975; 305: 480–4.

Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. J of Clin Neurophysiol 1999; 16: 341–52. [PubMed: 10478707]

Kilbride RD, Costello DJ, Chiappa KH. How seizure detection by continuous electroencephalographic monitoring affects the prescribing of antiepileptic medications. Arch Neurol 2009; 66: 723–8. [PubMed: 19506131]

Kim JA, Rosenthal ES, Biswal S, Zafar S, Shenoy AV, O'Connor KL, et al. Epileptiform abnormalities predict delayed cerebral ischemia in subarachnoid hemorrhage. Clin Neurophysiol 2017; 128: 1091–9. [PubMed: 28258936]

Kurtz P, Gaspard N, Wahl AS, Bauer RM, Hirsch LJ, Wunsch H, et al. Continuous electroencephalography in a surgical intensive care unit. Intensive Care Med 2014; 40: 228–34. [PubMed: 24240843]

Naidech AM, Kreiter KT, Janjua N, Ostapkovich N, Parra A, Commichau C, et al. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. Stroke 2005; 36: 583–7. [PubMed: 15662039]

Ney JP, Van Der Goes DN, Nuwer MR, Nelson L, Eccher MA. Continuous and routine EEG in intensive care Utilization and outcomes, United States 2005–2009. Neurology. 2013 12 3;81(23): 2002–8. [PubMed: 24186910]

Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. Critical Care Med 2009; 37: 2051–6 [PubMed: 19384197]

Payne ET, Zhao XY, Frndova H, McBain K, Sharma R, Hutchison JS, et al. Seizure burden is independently associated with short term outcome in critically ill children. Brain 2014; 137: 1429–38. [PubMed: 24595203]

Pearl PL, McCarter R, McGavin CL, Yu Y, Sandoval F, Trzcinski S, et al. Results of phase II levetiracetam trial following acute head injury in children at risk for posttraumatic epilepsy. Epilepsia. 2013 9 1;54(9).

Perucca P, Carter J, Vahle V, Gilliam FG. Adverse antiepileptic drug effects Toward a clinically and neurobiologically relevant taxonomy. Neurology 2009; 72: 1223–9. [PubMed: 19349601]

Ruiz AR, Vlachy J, Lee JW, Gilmore EJ, Ayer T, Haider HA, et al. Association of periodic and rhythmic electroencephalographic patterns with seizures in critically ill patients. JAMA Neurol 2017; 74: 181–8. [PubMed: 27992625]

Sivaraju A, Gilmore EJ. Understanding and managing the ictal-interictal continuum in neurocritical care. Curr Treat Options Neurol 2016; 18: 8. [PubMed: 26874841]

Struck AF, Westover MB, Hall LT, Deck GM, Cole AJ, Rosenthal ES. Metabolic correlates of the ictal-interictal continuum: FDG-PET during continuous EEG. Neurocrit Care 2016; 24: 324–31. [PubMed: 27169855]

Struck AF, Ustun B, Ruiz AR, Lee JW, LaRoche SM, Hirsch LJ, et al. Association of Electroencephalography- Based Risk Score with Seizure Probability in Hospitalized Patients. JAMA Neurol 2017; 74: 1419–24. [PubMed: 29052706]

Sutter R, Fuhr P, Grize L, Marsch S, Rüegg S. Continuous video-EEG monitoring increases detection rate of nonconvulsive status epilepticus in the ICU. Epilepsia. 2011 3 1; 52: 453–7. [PubMed: 21204818]

Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. Neurocrit Care. 2010 4 1;12(2):165–72. [PubMed: 19898966]

Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies. Stroke 2010;41:2391–5. [PubMed: 20798370]

Vespa P, Tubi M, Claassen J, Buitrago-Blanco M, McArthur D, Velazquez AG, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. Ann Neurol 2016; 79: 579–90. [PubMed: 26814699]

Witsch J, Frey HP, Patel S, Park S, Lahiri S, Schmidt JM, et al. Prognostication of long-term outcomes after subarachnoid hemorrhage: The FRESH score. Ann Neurol 2016; 80: 46–58. [PubMed: 27129898]

Witsch J, Frey H, Schmidt JM, Velazquez A, Falo CM, Reznik M, et al. Electroencephalographic Periodic Discharges and Frequency-Dependent Brain Tissue Hypoxia in Acute Brain Injury. JAMA Neurol 2017; 74: 301–309. [PubMed: 28097330]

Yoon SJ, Joo JY, Kim YB, Hong CK, Chung J. Effects of prophylactic antiepileptic drugs on clinical outcomes in patients with a good clinical grade suffering from aneurysmal subarachnoid hemorrhage. J Cerebrovasc Endovasc Neurosurg 2015; 17: 166–72. [PubMed: 26526008]

Zafar SF, Westover MB, Gaspard N, Gilmore E, Foreman B, O'Connor K, et al. Interrater Agreement for Consensus Definitions of Delayed Ischemic Events After Aneurysmal Subarachnoid Hemorrhage. Journal of Clinical Neurophysiology 2016;33:235–40. [PubMed: 27258447]

Zafar SF, Postma EN, Biswal S, Fleuren L, Boyle EJ, Bechek S, et al. Electronic Health Data Predict Outcomes After Aneurysmal Subarachnoid Hemorrhage. Neurocritical care 2017; 5: 1–0.

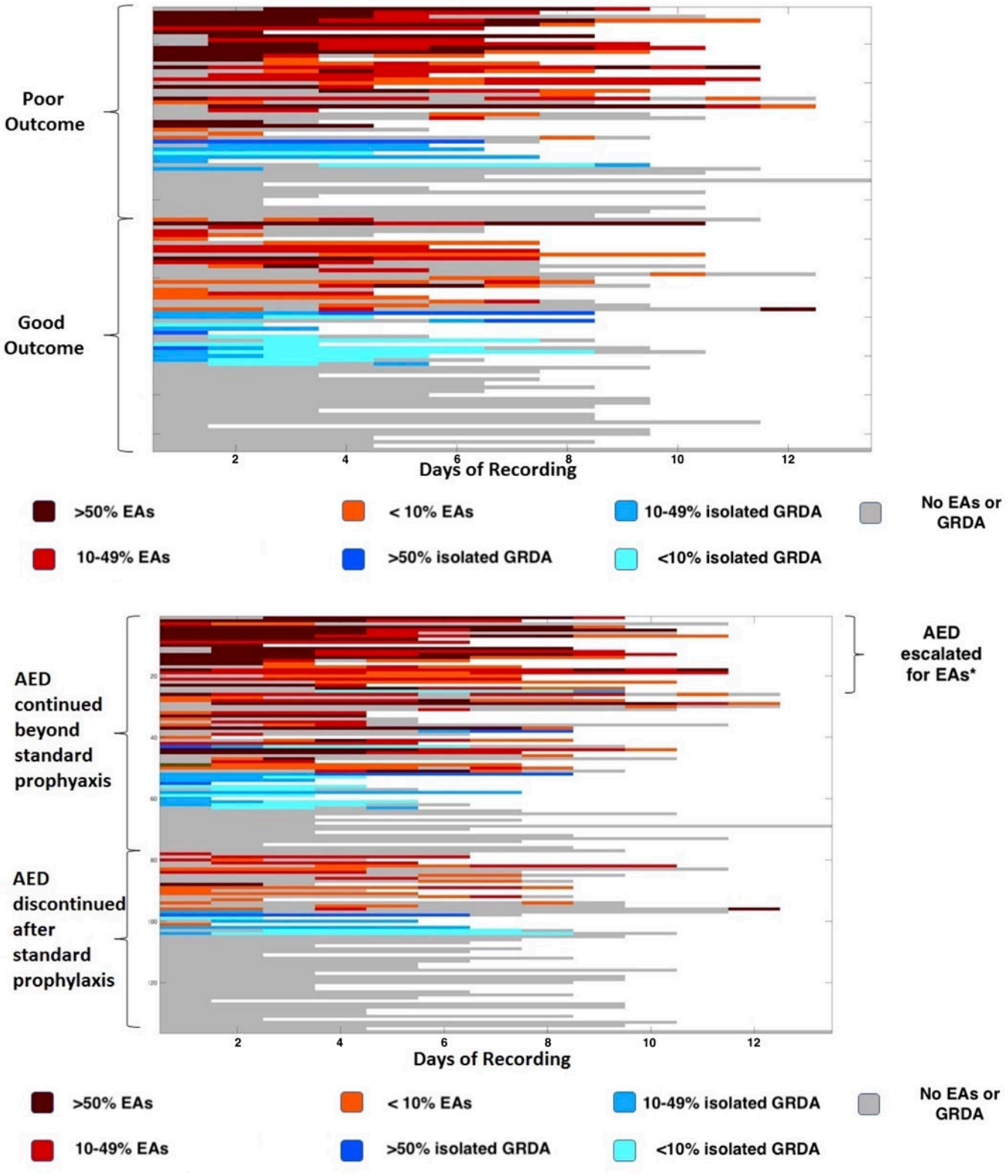
Zeiler FA, Teitelbaum J, Gillman LM, West M. NMDA antagonists for refractory seizures. Neurocritical care 2014; 20: 502–13. [PubMed: 24519081]

Significance:

EA burden predicts worse outcomes and may serve as a target for prospective interventional controlled studies to directly assess the impact of AEDs, and create evidence-based treatment protocols.

Highlights

- Higher epileptiform abnormality burden is associated with worse outcomes in subarachnoid hemorrhage.
- Epileptiform abnormalities are frequently treated with anti-epileptic drugs.
- Prospective studies are needed to delineate the clinical risks and benefits of treatment.



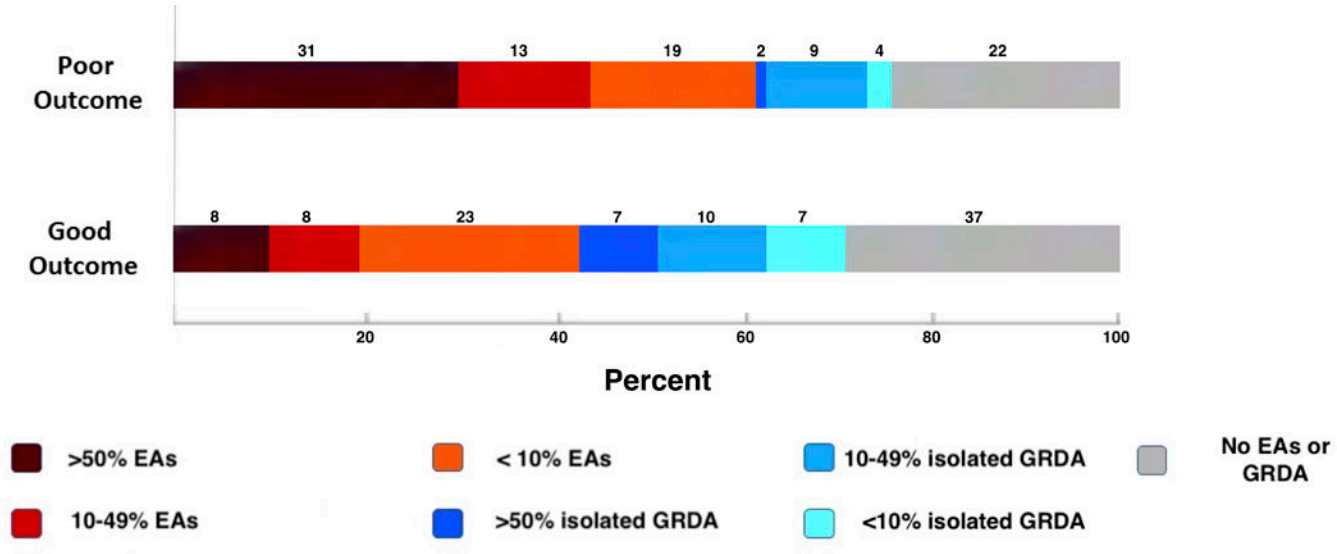


Figure 1. EA Burden, outcomes and treatment

A) Association of EA burden with neurologic outcome. EEG findings over days for 114 patients with 3 month neurologic outcomes. Each bar represents the EEG time course for one patient. The top half of the figure shows patients with poor outcome (GOS 1–3) and bottom half shows patients with good outcome (GOS 4–5). In addition there is a second ordering according to presence and burden of EAs and isolated GRDA, such that in each outcome group patients with EAs are shown on the top, followed by patients with isolated GRDA, and finally patients with neither EAs or GRDA. The figure shows that patients with higher EA burden are more likely to have poor neurologic outcomes. This impression is quantified in Figures 2 and 3, and Table 3.

B) Association of EA burden with AED treatment. EEG findings over days for 136 patients is shown. Each bar represents the EEG time course for one patient. The top half of the figure shows patients who underwent continued AED treatment beyond the standard prophylaxis protocol. The bottom half shows patients in whom AEDs were discontinued after standard prophylaxis. In addition there is a second ordering according to presence and burden of EAs and isolated GRDA, such that in each treatment group patients with EAs are shown on the top, followed by patients with isolated GRDA, and finally patients with neither EAs or GRDA.

*Additionally we highlight patients that had further AED escalation (dose increase or addition of alternate AEDs) specifically for scalp EAs. Patients with higher burden of EAs were more likely to undergo AED escalation. Patients with lower EA burden were less likely to have AED escalation.

C) Association of maximum daily EA burden with neurologic outcome. The proportion of patients with each burden group during the epoch with maximum daily burden is shown. A higher proportion of patients with poor outcomes have a maximum daily EA burden>50%.

AED: antiepileptic drugs; EAs: Epileptiform abnormalities GRDA: generalized rhythmic delta activity; LRDA: lateralized rhythmic delta activity, PD: periodic discharges.

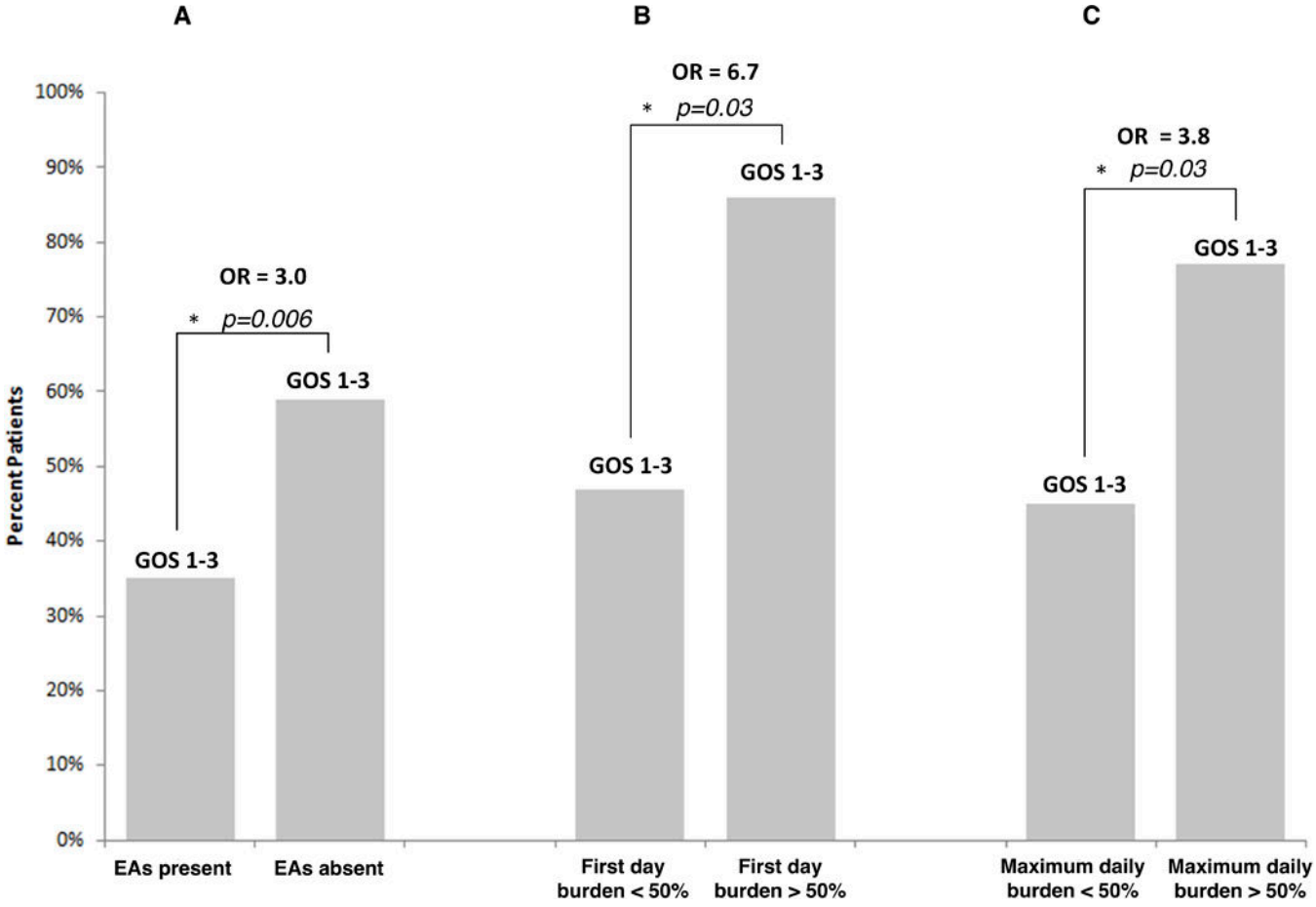


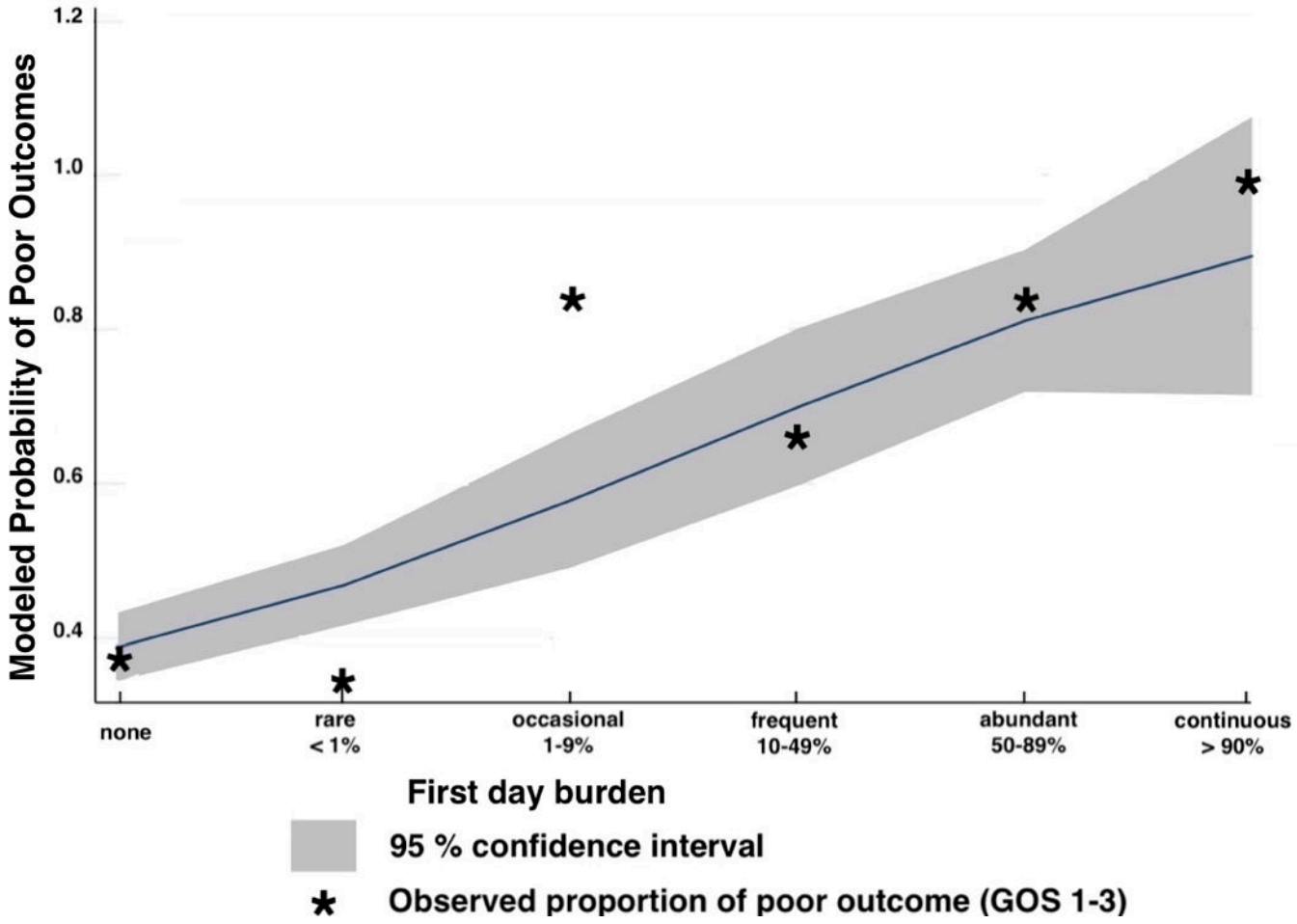
Figure 2. Differences in outcomes based on 3 ways of measuring EA burden: Univariate analyses.

A) Differences in outcomes between patients with EAs based on presence vs absence. 58.6% of patients (34/58) with EAs had poor outcomes (GOS 1–3) compared with 35.7 % (20/56) patients without EAs (p = 0.006).

B) Differences in outcomes among patients with EAs based on first day burden. 47.4 % of patients with a first day burden of < 50% had poor outcomes (GOS 1–3) compared with 85.7% of patients with a first day burden > 50% (p= 0.03).

C) Differences in outcomes among patients with EAs based on maximum daily burden. 47.2 % of patients with a maximum daily burden of < 50% had poor outcomes (GOS 1–3) compared with 77.2% of patients with a maximum daily burden > 50% (p= 0.03).

* statistically significant (P<0.05)



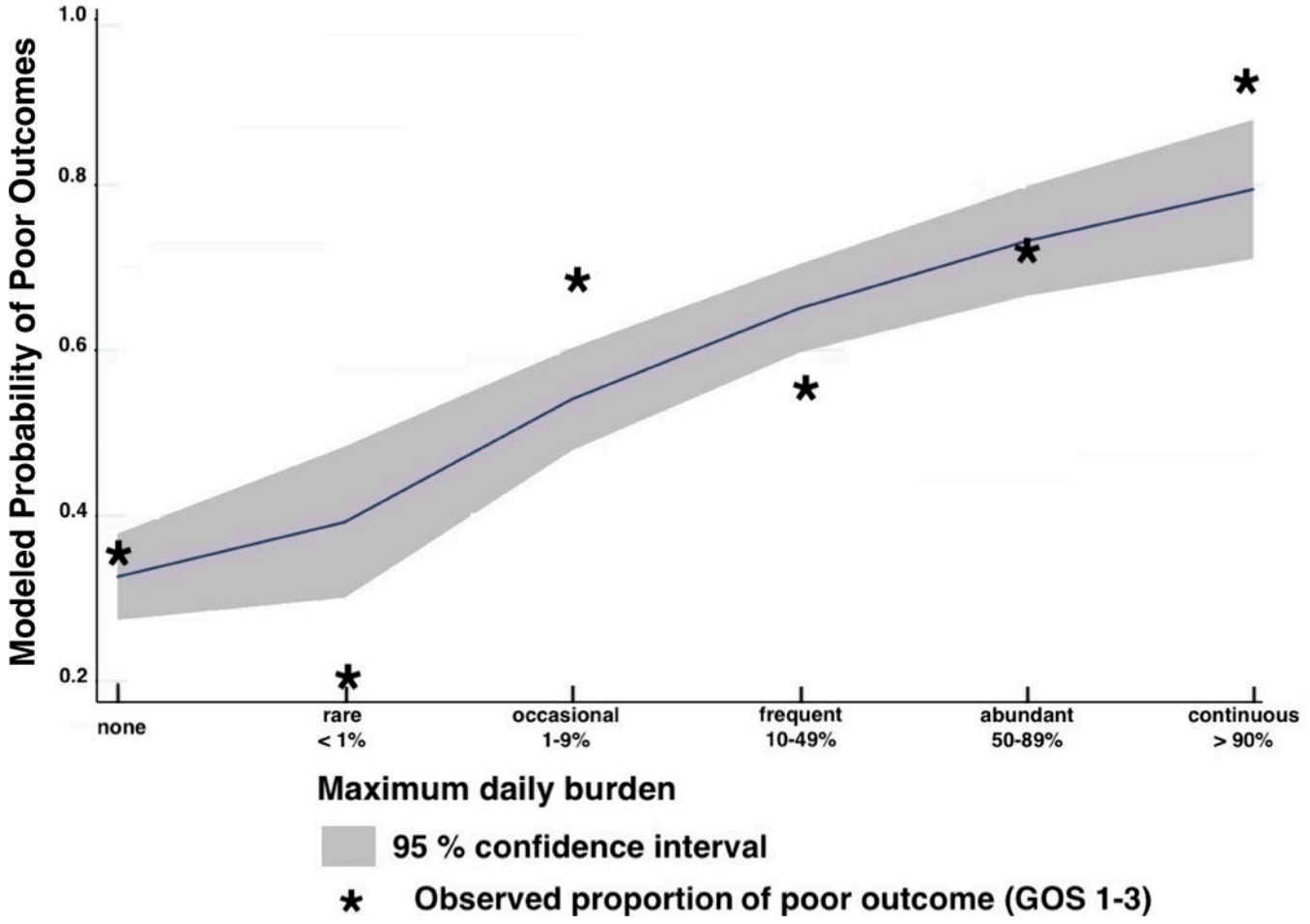


Figure 3. "Dose-response" relationship between poor outcome and EA burden: Multivariate analyses.

A) The figure shows the modeled probability of poor outcome (GOS 1–3) with increasing first day burden. This dose-response plot is obtained from the multivariate model, which includes as predictors age, gender, Hunt and Hess score, APACHE II score, delayed cerebral ischemia, re-bleed, hospital acquired pneumonia, and anti-epileptic drugs. The probability of poor outcomes increases with increasing first day burden. The shaded area represents the 95% confidence intervals of the model predictions. The average marginal effect for this model is an average 8% increased probability of poor outcome with each increasing EA burden category (Average marginal effect: 0.078, CI (0.024–0.132), p=0.005).

*Superimposed we show the actual observed proportion of poor outcome for each burden category, to allow assessment of agreement between observed proportions of poor outcomes and the proportions predicted by the model. While some variability is evident in the observed proportions, the overall monotonically increasing trend is clearly evident, suggest that the model adequately describes the data.

B) The figure shows the modeled probability of poor outcome (GOS 1–3) with increasing maximum daily burden. This dose-response prediction plot is obtained from the multivariate model after adjusting for age, gender, Hunt and Hess score, APACHE II score, delayed cerebral ischemia, re-bleed, hospital acquired pneumonia, and anti-epileptic drugs. The

probability of poor outcomes increases with increasing first daily maximum burden. The shaded area represents the 95% confidence band. The average marginal effect for this model is an average 7% increased probability of poor outcome with each increasing EA burden category (Average marginal effect: 0.070, CI (0.024–0.115), p=0.003).

*Superimposed we show the actual observed proportion of poor outcome for each burden category, to allow comparison between observed proportions of poor outcomes and the proportions predicted by the model. While there is some variability in the observed proportions, an overall monotonically increasing trend is clearly evident in the data, suggest that the model adequately describes the data.

APACHE II: Acute Physiology and Chronic Health Evaluation II

Table 1.

Clinical and Demographic variables.

	All patients (n=136)	**EAs present[a] (n=65)**	**EAs absent (n=71)**	**P value**
Age: median, (IQR)	57, (49–68)	62 (51–74)	54.5 [45–65]	**0.0030**
Gender: F (%)	96 (70.6%)	48(73.8%)	48(67.6%)	0.456
Apache II: median, (IQR)	14 (8–20)	18, (11.5–21.5)	11 (6–18)	**<0.0001**
Hunt and Hess score 1 2 3 4 5	29 (21.3%) 25 (18.4%) 30 (22.1%) 36 (26.5%) 16 (11.8%)	9 (13.8%) 10(15.4%) 15 (23.1%) 19(29.2%) 12(18.5%)	20 (28.2%) 15 (21.1%) 15(21.1%) 17(23.9%) 4 (5.6%)	**0.035[b]**
Fisher 1 2 3 4	1 (0.74%) 9 (6.6%) 103 (75.7%) 23 (16.9%)	0 (0.00%) 4 (6.06%) 48 (74.2%) 13 (19.7%)	1(1.42%) 5(7.14%) 55(77.1%) 10(14.3%)	0.747[c]
EEG duration (days): median, (IQR)	6.8 (4.7–8.8)	7.7, (5.7– 9.4)	5.9, (3.8– 8.1)	**0.0063**
Seizure on presentation	22 (16.2%)	8(12.3%)	13(18.3%)	0.354
AED continued beyond prophylaxis protocol	77 (56.7%)	46 (70.8%)	31 (43.7%)	**0.002**
AED on discharge	41/113 (36.3%)	25/48 (52.1%)	16/65 (24.6%)	**0.003**
Treatment modality Coil Clip Coil and clip Flow diverter Flow diverter +coil None	67(49.3%) 40(44.1%) 3 (2.21%) 3 (2.21%) 1 (0.74%) 2 (1.47%)	31 (55.4%) 30 (46.2%) 2 (1.54%) 1 (3.07%) 0 (1.54%) 1 (1.54%)	36 (43.7%) 30 (42.3%) 1 (2.81%) 2 (1.4%) 1 (0.00%) 1 (1.4%)	0.6096[d]
DCI	68(50%)	43/65(65.1%)	25/71(35.2%)	**0.001**
HAI	78(57.4%)	43 (66.2%)	35(49.3%)	0.057
HAP	56 (41.2%)	34(52.3%)	22(31.0%)	**0.015**
Duration of MV days: median, (IQR)	3 (0–10)	7 (2–12.5)	1 (0–7)	**<0.0001**
ICU length of stay: median (IQR)	15 (11–19)	16 (12–19.5)	14 (10–17)	0.0545

a) EAs excluding GRDA

b) Hunt and Hess 1–3 versus Hunt and Hess 4–5

c) Fisher 1–2 versus Fisher 4–5

d) Endovascular versus open surgical treatment

AED: anti-epileptic drug; DCI: delayed cerebral ischemia; EAs: epileptiform abnormalities; EEG: electroencephalogram; HAI: hospital acquired infections; HAP: hospital acquired pneumonia; MV: mechanical ventilation

Table 2.

Continuous EEG features

Overall prevalence of EEG patterns	**N (% of 136)**
Overall prevalence	90 (66.2%)
Electrographic seizures	6 (4.4%)
Lateralized periodic discharges (LPDs)	14 (10.3%)
Bilateral independent periodic discharges (BIPDs)	5 (3.68%)
Generalized periodic discharges (GPDs)	15 (11.0%)
Lateralized rhythmic delta activity (LRDA)	20 (14.7%)
Generalized rhythmic delta activity (GRDA)	52 (38.2%)
Sporadic discharges	65 (47.8%)
Most prevalent EAs in epoch with max daily burden (excluding GRDA)	N (% of 65)
Electrographic seizures	1 (1.5%)
LPDs	12 (18.5%)
BIPDs	5 (7.7%)
GPDs	8 (12.3%)
LRDA	13 (20.0%)
Sporadic discharges	26 (40.0%)
First day burden[a]	N (% of 65)
None	27 (41.5%)
Rare	10 (15.4%)
Occasional	7 (10.8%)
Frequent	5 (7.7%)
Abundant	12 (18.5%)
Continuous	4 (6.2%)
Maximum daily burden [b]	N (% of 65)
Rare (<1%)	12 (18.5%)
Occasional (1– 9%)	13 (20.0%)
Frequent (10–49%)	14 (21.5%)
Abundant (50–89%)	16 (24.6%)
Continuous (>90%)	10 (15.4%)

a) EA burden in the first 18–24 hour epoch

b) 18–24 hour epoch with the maximum daily burden of EAs.

EAs: epileptiform abnormalities

Table 3.

EA burden and 3 month outcomes: Multivariate analysis

EA burden	Odds Ratio	Confidence Interval	P value*
EAs present	2.2	0.9 – 5.8	0.086[a]
First day burden >10% vs < 10%	4.1	1.1 – 14.7	**0.028**[b]
First day burden > 50% vs < 50%	6.6	1.3 – 34.5	**0.025**[c]
Maximum daily burden >10% vs < 10%	4.5	1.6 – 12.7	**0.004**[d]
Maximum daily burden > 50% vs < 50%	5.3	1.5 – 18.3	**0.008**[e]

*Adjusted for age, gender, Hunt and Hess Score, APACHE II score, re-bleed, delayed cerebral ischemia, hospital acquired pneumonia, anti-epileptic drugs

[a]Hosmer-Lemeshow chi-square2 with 8 degrees of freedom=5.85, p=0.66 (acceptable model fit)

[b]Hosmer-Lemeshow chi-square2 with 8 degrees of freedom=8.39, p=0.40 (acceptable model fit)

[c]Hosmer-Lemeshow chi-square2 with 8 degrees of freedom=7.76, p=0.46 (acceptable model fit)

[d]Hosmer-Lemeshow chi-square2 with 8 degrees of freedom=12.8, p=0.12 (acceptable model fit)

[e]Hosmer-Lemeshow chi-square2 with 8 degrees of freedom=7.32, p=0.50 (acceptable model fit)

EAs: Epileptiform abnormalities