



Anti-seizure medication treatment and outcomes in acute ischemic stroke patients undergoing continuous EEG monitoring

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Abstract

Objectives To determine the association of anti-seizure medication (ASM) treatment with outcomes in acute ischemic stroke (AIS) patients undergoing continuous electroencephalography (cEEG).

Methods Retrospective analysis of AIS patients admitted between 2012 and 2019. The following are the inclusion criteria: age ≥ 18 years and ≥ 16 h of cEEG within the first 7 days of admission. ASM treatment exposure was defined as > 48 h of treatment after the first 24 h of cEEG. The primary outcome measure was 90-day mortality, and the secondary outcome was 90-day functional recovery (Modified Ranking Scale 0–3). Propensity scores were used to adjust for baseline covariates and presence of epileptiform abnormalities (seizures, periodic and rhythmic patterns).

Results One hundred thirteen patients met the inclusion criteria; 39 (34.5%) were exposed to ASM. ASM treatment was not associated with 90-day mortality (propensity adjusted HR 1.0 [0.31–3.27], $p = 0.999$) or functional outcomes (adjusted HR 0.99 [0.32–3.02], $p = 0.989$), compared to no treatment.

Conclusions In our study, ASM treatment in AIS patients with cEEG abnormalities was not significantly associated with a change in 90-day mortality and functional recovery. Larger comparative effectiveness studies are indicated to identify which acute ischemic stroke patients with cEEG abnormalities benefit most from ASM treatment.

Keywords Ischemic stroke · Seizure · Epileptiform abnormalities · Anti-seizure medications · Outcomes

The study was approved by the Institutional Review Board of Mass General Brigham.

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Introduction

Continuous electroencephalography (cEEG) is often utilized for the detection of electrographic seizures in patients with acute ischemic stroke and a clinical concern for seizures or unexplained encephalopathy [1–3]. Epileptiform abnormalities (EAs), including seizures and periodic and rhythmic patterns, can be seen in up to 40% of patients presenting with post-stroke neurological deterioration [4]. Prior studies have shown conflicting results on whether EAs are associated with worse discharge outcomes in patients with acute ischemic stroke [1, 3]. At the same time, anti-seizure medications (ASMs) are frequently prescribed in response to cEEG findings, and there is limited evidence on whether treatment improves outcomes [1, 3]. The goal of this study was to describe ASM treatment patterns and estimate the effect of treatment on 3-month mortality and functional outcomes, in AIS patients undergoing cEEG monitoring.

Methods

This is a retrospective cohort study of patients with AIS admitted to a single center between January 2012 and December 2019. The study was approved by the Institutional Review Board. Informed consent was not required. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies [5]. The data that support the findings of this study are available from the senior author upon reasonable request.

The inclusion criteria were (1) admission for acute ischemic stroke, (2) age > 18 years, (3) cEEG monitoring initiated within 7 days of admission, and (4) ≥ 16 h of cEEG monitoring. We restricted our cEEG exposure to the first 7 days of admission as this defines the risk period for acute symptomatic seizures [6, 7]. We restricted our inclusion criteria to patients with 16 h of cEEG as the probability of seizures drops to < 5% if no seizures have occurred in the first 16 h of recording [8]. We excluded patients with prior diagnosis of epilepsy or those on chronic ASM treatment prior to admission for AIS. We also excluded patients admitted for less than 7 days.

ASM treatment exposure definition

Indications for ASM treatment included clinical seizures and EAs. ASM type, dosage, and duration of treatment were at the discretion of the treating team. We defined ASM treatment exposure as the initiation or continuation of ASMs for ≥ 48 h after the first 24 h of cEEG and through day 7 of admission. The unexposed group consisted of patients who did not receive any ASMs or received less than 48 h of ASM exposure within the first 7 days of admission. Follow-up for outcomes started after day 7 of admission and continued in an intention-to-treat scheme until 90 days from start of follow-up.

Clinical covariates

Demographic and clinical variables were abstracted from the electronic health record. Comorbidities were quantified using the Charlson Comorbidity Index (CCI) [9]. We measured stroke severity using the NIH Stroke Scale (NIHSS) [10], and critical illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE II) score [11]. Stroke etiology was classified using the Trial of ORG 10,172 in acute stroke treatment (TOAST) criteria [12]. Stroke location was characterized based on cortical involvement and vascular territory involved. Stroke treatment modality (i.e., intravenous thrombolysis and/or intra-arterial thrombectomy) was recorded. Occurrence of post-stroke complications including hemorrhagic transformation, need for

decompressive craniectomy, and hospital-acquired infections were also recorded.

cEEG recording and features

The primary indications for cEEG monitoring were screening for non-convulsive seizures (NCS) and unexplained altered mental status. Continuous video EEG was recorded using 21 electrodes and the International 10–20 system. Two clinical neurophysiologists reviewed and reported the cEEG findings at least twice daily during the hospitalization. All cEEG findings were reported using the American Clinical Neurophysiology Society nomenclature (ACNS) [13]. cEEG features and EA burden data were abstracted from the clinical EEG reports.

Epileptiform abnormalities (EAs) were defined as any of the following patterns: electrographic seizures, lateralized periodic discharges (LPDs), generalized periodic discharges (GPDs), bilateral independent periodic discharges (BiPDs), and lateralized rhythmic delta activity (LRDA). Electrographic seizures were defined as spikes and sharp wave or sharp-slow wave complexes lasting for 10 s or more at a frequency of 3 Hz or at a frequency of 1 Hz but with clear evolution in frequency, morphology, or location [14]. Generalized rhythmic delta activity (GRDA) and sporadic discharges are not associated with a high risk for poor outcomes and hence were excluded from our definition of EAs [3, 15].

EA burden was quantified using the ACNS terminology: rare < 1%, occasional 1–9%, frequent 10–49%, abundant 50–89%, or continuous > 90% [13]. We quantified the EA burden as follows:

- 1) First 24 h EA burden—defined as the percentage of the first 24 h of recording occupied by EAs. For patients with less than 24 h of recording, all available cEEG data was considered as the first 24-h epoch.
- 2) Peak EA burden—defined as maximum EA burden measured within any 12-h window. Peak EA burden was calculated as the percentage of the 12-h epoch occupied by EA patterns.

Primary and secondary outcomes

Our primary outcome measure was 90-day mortality. The secondary outcome was 90-day functional recovery (good outcome) as measured by the Modified Rankin Scale (mRS): 0, no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death [16]. For analysis, we dichotomized functional status into good outcome (mRS of 0 to 3) or poor (mRS of 4 to 6). mRS was abstracted from physician and physical and occupational therapy clinical examinations by two reviewers (PS and SFZ) who were blinded to the EEG findings and ASM treatment exposure status at the time

of outcome abstraction. Additionally, we examined the time to late onset clinical seizures, defined as seizures occurring after day 7 of admission [17].

Statistical analysis

Fisher's exact test was used for comparison of 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. Equality of survival functions was assessed using the log-rank test.

We used propensity score–adjusted analysis to address the potential clinical differences between ASM treatment exposed and non-exposed patients. The propensity score regression model included variables likely to be associated with ASM treatment, acute symptomatic seizures, and poor outcomes [3, 18–22]. These variables included NIHSS, APACHE II score, CCI, acute stroke treatment (thrombolysis and/or thrombectomy), clinical seizures on presentation, and first 24-h EA burden. We selected variables that captured illness severity, EEG findings, and comorbidities and were measured prior to the exposure window. The area under the receiver operating curve (ROC) for the propensity score model was 0.92. The estimated propensity score was included in a Cox proportional hazard model to assess the association between ASM treatment and primary and secondary outcomes. The proportional hazards assumption was evaluated using Schoenfeld residuals and log–log survival plots. Hazard ratios are presented with 95% confidence intervals as HR [95% CI]. Patients lost to follow-up were right censored in the analysis.

Results

During the study period, there were on average 825 ischemic stroke admissions per year (range 790–895/year). One hundred thirteen patients met the inclusion criteria. Thirty-nine (34.5%) patients received ASM treatment exposure, and 74 (65.5%) were non-exposed. Table 1 summarizes the clinical and demographic characteristics of this cohort. There were no missing data. There were no significant differences in NIHSS, APACHE II score, and rates of hemorrhagic transformation and hemicraniectomy between the two groups. Patients receiving ASM exposure were monitored with cEEG for longer duration and were more likely to have clinical seizures and higher first 24-h and peak EA burden.

Patients with ASM exposure received a median of 9 days of inpatient ASM treatment (IQR 6–19). Among treatment-exposed patients, 37 (94.9%) received levetiracetam treatment, 7 (17.9%) received phenytoin, 4 (10.3%) received lacosamide, and 3 (7.7%) received valproic acid (these percentages are not mutually exclusive). Eleven patients in the unexposed group received < 48 h of ASM (levetiracetam

only) treatment. In all eleven unexposed patients, ASMs were initiated due to an initial clinical concern for seizures and discontinued within 48 h of cEEG monitoring. Of the 33 ASM treatment-exposed patients alive at discharge, 24 (72.7%) were discharged with ASM prescriptions.

Primary and secondary outcomes

Figure 1 shows the Kaplan–Meier and adjusted survival curves. At 90 days, mortality was 7/39 (18%) in the ASM treatment-exposed group and 23/74 (31%) in the non-exposed group. Twenty-five of 30 (83.3%) patients who died had withholding of life-sustaining therapy or were discharged to hospice. The unadjusted HR for 90-day mortality in the ASM treatment-exposed group was 0.55 [0.23–1.28]. After adjusting for the propensity score, the HR was 1.0 [0.31–3.27].

Figure 2 shows the Kaplan–Meier and adjusted curves for good outcomes defined as mRS 0–3. At 90 days, 10 (26%) patients in the ASM treatment-exposed group had good functional outcomes vs. 29 (39%) in the non-exposed group. The unadjusted HR for good functional outcome in the ASM treatment group was 1.19 [0.53–2.69] compared to the non-exposed group. After adjusting for the propensity score, ASM treatment exposure was not significantly associated with functional outcomes: HR 0.99 [0.32–3.02]. Survival data, including loss to follow-up rates, are summarized in Supplementary Tables S1 and S2.

Three patients in the ASM treatment-exposed group had late seizures, compared with 2 patients in the unexposed group.

Sensitivity analysis

In a sensitivity analysis, we excluded all patients with clinical seizures on admission as these patients have a higher likelihood of being continued on ASMs regardless of cEEG findings. After exclusion of patients with clinical seizures, the ASM exposure arm only included patients in whom treatment was prescribed in response to cEEG findings. In this analysis, there continued to be no significant association between ASM treatment exposure and 90-day mortality (propensity adjusted HR 0.77 [0.023–2.66], *p* = 0.70) or functional outcomes (propensity adjusted HR 0.49 [0.09–2.80], *p* = 0.42).

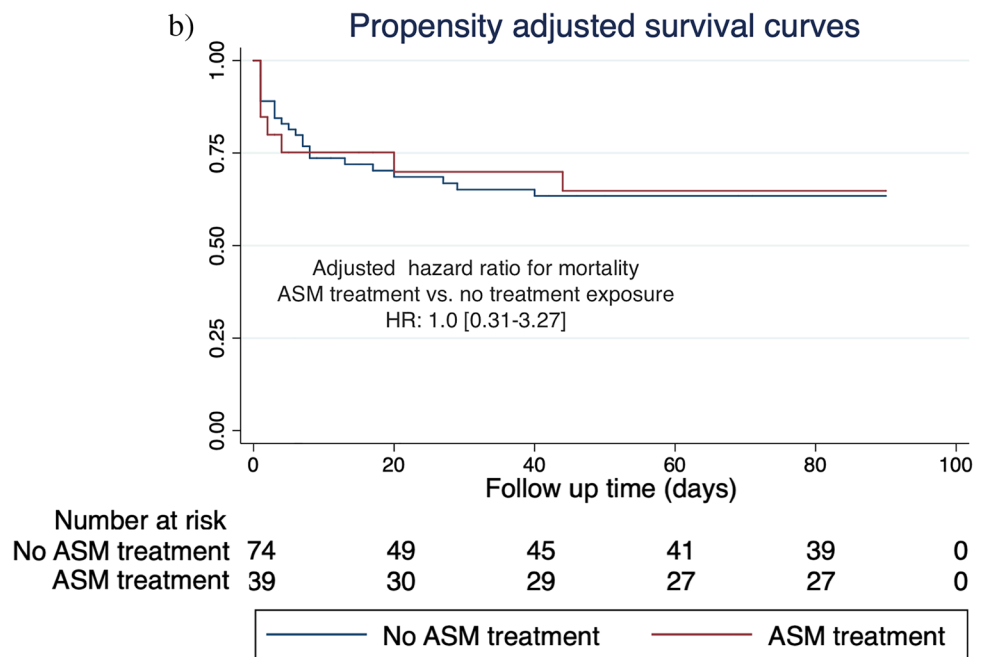
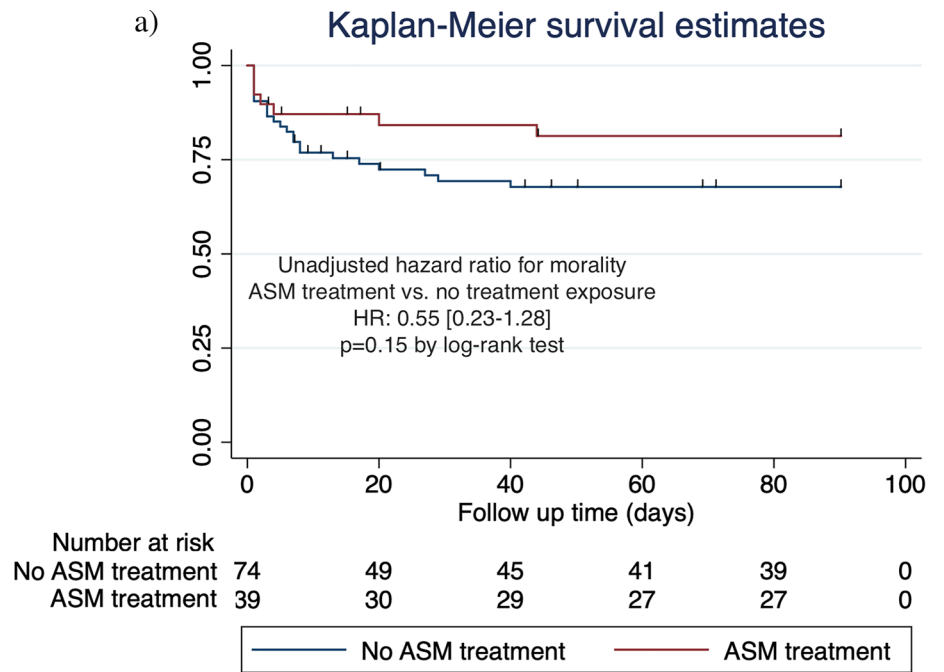
In an additional sensitivity analysis, we excluded the 11 patients with < 48 h of ASM treatment in the unexposed group. In this analysis, ASM treatment exposure was not significantly associated with mortality (HR 0.539 [0.21–1.36], *p* = 0.184) or functional outcomes (HR 1.44 [0.66 [0.59–3.52]], *p* = 0.425). Finally, we performed a sensitivity analysis using fewer covariates in the propensity score model to address any potential impact of over fitting in the main propensity model and found no difference in our primary results (supplemental material).

Table 1 Clinical and demographic characteristics

	ASM treatment exposure, <i>N</i> = 39 (34.5%)	No ASM treatment exposure, <i>N</i> = 74 (65.5%)	<i>p</i> -value
Age, median (Q1–Q3)	68 (60–76)	69 (56–77)	0.9110
Gender, female (%)	22 (56.4)	36 (48.6)	0.5529
CCI, median (Q1–Q3)	4 (3–6)	2 (2–6)	0.7843
NIHSS, median (Q1–Q3)	12 (7–23)	14 (9–18)	0.7856
APACHE II, median (Q1–Q3)	18 (13–25)	17 (12–22)	0.6328
Stroke etiology			0.927
Large-artery	8 (20.5%)	21 (28.3%)	
Cardioembolic	20 (51.3%)	33 (44.6%)	
Small-vessel	2 (5.1%)	5 (6.8%)	
Other determined etiologies	4 (10.3%)	7 (9.6%)	
Undetermined	5 (12.8%)	8 (10.8%)	
Stroke location			
Cortical	32(82.1%)	60 (81.1%)	1.000
Subcortical	7 (17.9%)	14 (18.9%)	
Anterior circulation	33 (84.6%)	57 (77.0%)	0.531
Posterior circulation	6 (15.4%)	14 (18.9%)	
Multiple vascular territories	0 (0.0%)	3 (4.1%)	
Stroke treatment modality			
Intravenous thrombolysis	7 (17.9%)	17 (23.0%)	0.357
Intra-arterial thrombectomy	3 (7.7%)	17 (23.0%)	0.0647
Hemorrhagic transformation	10 (25.6%)	24 (32.4%)	0.522
Hemicraniectomy	4 (10.3%)	6 (8.1%)	0.735
Clinical seizures on presentation	17 (43.6%)	2 (2.7%)	<0.0001
cEEG duration in hours, median (Q1–Q3)	42 (24–50)	24(21–28)	0.0002
cEEG findings			
Electrographic seizures	11 (28.2%)	0 (0.0%)	<0.0001
Lateralized periodic discharges	18 (46.2%)	13(76.6%)	0.002
Generalized periodic discharges	8 (20.5%)	6 (8.1%)	0.074
Lateralized rhythmic delta activity	2 (5.1%)	5 (6.8%)	1.000
Generalized rhythmic delta activity	10 (25.6%)	12 (16.2%)	0.317
Sporadic discharges	6 (15.4%)	10 (13.5%)	0.744
First 24-h epileptiform abnormality burden			<0.0001
None	10 (25.6%)	52 (70.3%)	
Rare (< 1%)	7 (17.9%)	0 (0.0%)	
Occasional (1–9%)	4 (10.3%)	11 (14.9%)	
Frequent (10–49%)	10 (25.6%)	8 (10.8%)	
Abundant (50–89%)	5 (12.8%)	2 (2.7%)	
Continuous (≥ 90%)	3 (7.7%)	1 (1.4%)	
Peak epileptiform abnormality burden			<0.0001
None	9 (23.1%)	52 (70.3%)	
Rare (< 1%)	7 (17.9%)	0 (0.0%)	
Occasional (1–9%)	3 (7.7%)	11 (14.9%)	
Frequent (10–49%)	9 (23.1%)	8 (10.8%)	
Abundant (50–89%)	6 (15.4%)	2 (2.7%)	
Continuous (≥ 90%)	5 (12.8%)	1 (1.4%)	
Hospital-acquired pneumonia	4 (10.3%)	17 (23.0%)	0.129
Tracheostomy	9 (23.1%)	7 (9.5%)	0.085
Percutaneous gastrostomy	13 (33.3%)	24 (32.4%)	1.000
Length of hospital stay (days)	13 (9–25)	16 (10–27)	0.3170

ASM anti-seizure medication, CCI Charlson Comorbidity Index, APACHE II Acute Physiology and Chronic Health Evaluation II, NIHSS National Institutes of Health Stroke Scale

Fig. 1 Ninety-day mortality. **a** Kaplan–Meier curves for time to death comparing ASM treatment exposure (red curve) vs. non-exposure (blue curve) in acute ischemic stroke patients undergoing cEEG monitoring. **b** Propensity-adjusted survival curves for time to death comparing ASM treatment exposure (red curve) vs. non-exposure (blue curve) in acute ischemic stroke patients undergoing cEEG monitoring. ASM, anti-seizure medication; cEEG, continuous electroencephalography



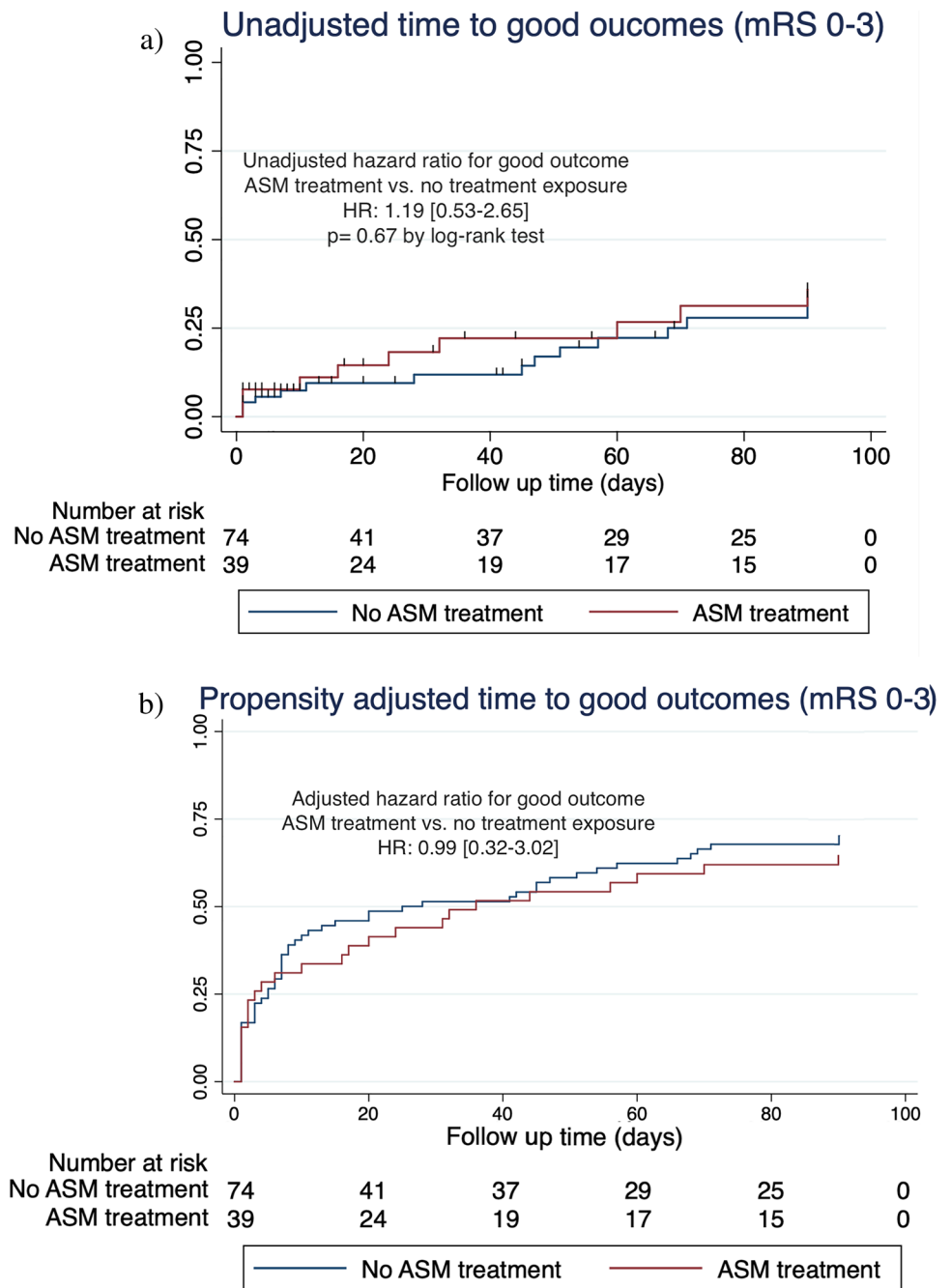
Discussion

In our cohort of acute ischemic stroke patients undergoing cEEG monitoring, sustained exposure to ASMs was not associated with significant changes in mortality or functional outcomes. Our study also demonstrated the utility of early cEEG for the characterization of clinical symptoms

concerning for seizures and de-escalation of unnecessary and potentially harmful ASM treatment in stroke.

Concerning EA, not all patterns may warrant sustained or high-dose ASM treatment. Within acute ischemic stroke patients, there are conflicting reports on the impact of EAs on outcomes [1, 3]. In one study of 132 acute ischemic stroke patients, EAs were not associated with worse discharge outcomes [1]. However, the authors did not quantify

Fig. 2 Ninety-day functional recovery. **a** Kaplan–Meier curves for time to good functional outcome (mRS 0–3) comparing ASM treatment exposure (red curve) vs. non-exposure (blue curve). **b** Propensity adjusted curves for time to good functional outcome (mRS 0–3) comparing ASM treatment exposure (red curve) vs. non-exposure (blue curve)



and account for EA burden. In 143 acute ischemic stroke patients, we have previously shown that increasing EA burden was associated with worse discharge functional outcomes [3]. Additionally, in prior work, we have demonstrated increasing burden of epileptiform abnormalities is associated with worse discharge outcomes across a larger cohort of medical, surgical, and neurological patients [23]. All aforementioned studies have shown frequent prescription of ASMs in patients with EAs [1, 3, 23]. Future randomized studies including acute ischemic stroke patients with high burden EAs, and excluding low burden EAs, could provide

evidence on the impact of ASM treatment on outcomes. Furthermore, such studies should evaluate long-term outcomes in multiple domains including functional, cognitive, and health-related quality of life.

In addition to a clear clinical correlate and high burden, EA pattern type, and frequency can also serve as potential treatment targets in future studies [24]. Specifically, prospective studies investigating the impact of ASM treatment on both seizure risk and outcomes in patients with high frequency (> 1.5 Hz) LPDs, GPDs, and LRDA are warranted as these patterns have the highest association with both seizures

and secondary brain injury [15, 25]. Periodic discharges are associated with metabolic stress as evidenced by markers of brain metabolism including reduction in brain tissue oxygenation, elevation in lactate/pyruvate ratio, and PET hypermetabolism [25–27]. Biomarker-guided treatment may also help optimize the potential impact of ASM on long-term outcomes.

Within our cohort, majority of patients with treatment exposure were also discharged on ASMs (72.7% of all treatment exposed patients). A similar finding of long-term continuation of ASMs in stroke patients with EAs has been reported in another study [28]. ASMs have the potential to impair functional and cognitive recovery in neurocritical care patients as highlighted by several studies [29, 30]. ASMs can also impair neurocognitive recovery and affect the quality of life of patients with post-stroke epilepsy (PSE) [31–33]. Therefore, further work is needed to investigate the proposed benefit of treatment during the acute phase and timely discontinuation or reduction of ASMs in the post-acute phase [34]. The post-acute symptomatic seizure (PASS) clinic model provides continuity of care for such patients and ensures appropriate ASM weaning when long-term treatment is not warranted [35]. A single-center PASS clinic model resulted in the reduction or discontinuation of ASMs in 44.6% of patients [35].

An indication for cEEG is the characterization and diagnostic clarification of paroxysmal events concerning for seizures [36]. Our study highlights the utility of cEEG for this indication in patients with acute ischemic stroke. In our cohort, 11 patients in the unexposed group were initially started on ASMs for clinical concern, with discontinuation shortly after initiation of cEEG monitoring. All 11 patients (10% of the total cohort) received ASMs for < 48 h and were therefore counted in the unexposed group. In a separate cohort of acute ischemic stroke patients, cEEG-guided de-escalation of treatment was reported in 4.5% of patients [1]. Paroxysmal events including rhythmic and repetitive motor movements, tremors, gaze deviation, and autonomic symptoms are frequently encountered in neurocritical care [37, 38]. These paroxysmal symptoms are not always seizures but can be misdiagnosed as seizures resulting in initiations of ASMs [37, 38]. In such patients, risk of ASM adverse effects outweigh benefits and cEEG data can provide guidance on discontinuation of unnecessary treatment.

Limitations of our study include the lack of randomization and the use of information from a single-center which may limit generalizability. There was limited sample size and number of patients in the exposed group. Our study may, therefore, be underpowered to find smaller differences. Restricting the eligibility criteria to 16 h of cEEG, may create a selection bias. Our cohort was also restricted to patients with higher stroke severity given our eligibility criteria of admission length ≥ 7 days, and need for prolonged cEEG.

Finally, although we used propensity scores, our results may still be prone to residual or unmeasured confounding.

In conclusion, acute ischemic stroke patients undergoing cEEG monitoring are often exposed to ASM treatment. However, it is unclear whether ASM treatment improves the outcomes. In our study, we found no significant differences in the outcomes between patients exposed to ASMs vs. not. Future larger comparative effectiveness studies and randomized investigations are indicated to identify patients that may benefit the most from ASM treatment and to define the optimum duration of treatment. Further work is also needed to determine whether cEEG-guided de-escalation of treatment in patients with a clinical concern for seizures could minimize the harmful effects of ASMs, such as cognitive impairment and sedation, and improve outcomes.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10072-022-06183-9>.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by PRS, MT, and SFZ. The first draft of the manuscript was written by PRS and SFZ. All authors commented on, edited, and revised the previous and final versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethical approval None.

Conflict of interest Dr. Zafar is a clinical neurophysiologist for Corticare, unrelated to this work. Dr. Rosenthal received consulting fees from UCB Pharma, Inc. and Ceribell, Inc., unrelated to this work. Dr. Westover is cofounder of Beacon Biosignals unrelated to this work.

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