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ORIGINAL WORK

Real-World Antiseizure Medication Prophylaxis and Outcomes in Hospitalized Adults with Acute Brain Injuries

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Abstract

Background: There is low-quality evidence for antiseizure medication (ASM) prophylaxis in acute brain injuries. We examined ASM prophylaxis patterns and explored the association with hospital outcomes in acute brain injury.

Methods: We analyzed the PINC AI Healthcare Database with data from more than 1,400 US hospitals. We included adults aged ≥ 18 years admitted for at least 2 days with acute brain injury (*International Classification of Diseases* codes for ischemic stroke [IS], hemorrhagic stroke [HS], and traumatic brain injury [TBI]) and excluded potential prevalent users and patients with epilepsy/seizures. Index date was the second day of admission. The ASM prophylaxis cohort received levetiracetam or phenytoin on the index date; the control cohort did not receive any ASM on the index date. Outcomes were time-to-mortality and time-to-home discharge.

Results: In total, 739,213 patients were eligible: 568,254 with IS, 86,842 with HS, and 84,117 with TBI. ASM prophylaxis was prescribed in 10,959/568,254 (2%) patients with IS, 31,970/86,842 (37%) patients with HS, and 38,331/84,117 (46%) patients with TBI. Patients on prophylaxis more frequently received mechanical ventilation, craniectomies/craniotomies, vasopressors, and anesthetics. After adjusting for markers of illness severity, prophylaxis was associated with mortality (IS: hazard ratio [HR] 2.02, 95% confidence interval [CI] 1.89–2.16; HS: HR 0.83; 95% CI 0.79–0.87; TBI: HR 0.97, 95% CI 0.89–1.06). Prophylaxis was associated with lower home discharge (IS: HR 0.40, 95% CI 0.37–0.42; HS: HR 0.61, 95% CI 0.58–0.64; TBI: HR 0.69, 95% CI 0.68–0.72). Across all acute brain injuries, mechanical ventilation exhibited strong association with outcomes.

Conclusions: Antiseizure medication prophylaxis was higher in TBI and HS compared with IS. Markers of illness severity (e.g., mechanical ventilation, neurosurgical procedures) were associated with more frequent prophylaxis. Prophylaxis exhibited differential associations with mortality (higher in IS, lower in HS and TBI). Prophylaxis was associated with lower home discharge across all acute brain injuries. We hypothesize that neurologic severity and critical illness severity are primary drivers of outcomes. However, the independent association of ASMs with outcomes warrants further investigation.

Keywords: Antiseizure medications, Seizure prophylaxis, Acute brain injuries, Electroencephalography, Acute symptomatic seizures

Introduction

Patients with acute brain injuries, such as ischemic and hemorrhagic stroke (HS) and traumatic brain injury (TBI), are at risk for acute symptomatic seizures, with reported incidence ranging from 3 to 18% [1–3]. Consensus guidelines report low quality of evidence for

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antiseizure medication (ASM) use in patients with brain injuries and make recommendations against primary antiseizure prophylaxis in stroke or recommendations for brief duration and electroencephalography-guided prophylaxis in, for example, trauma and subarachnoid hemorrhage [4–7]. The recommendations vary across brain injury types and are made with a low level of certainty [4–7]. At the same time, in patients with acute brain injuries, use of ASMs has been shown to be associated with worse cognitive and functional outcomes [8–11]. ASMs also result in additional adverse events, including falls and metabolic and cardiac complications [12–15]. The limited data available to guide management likely result in wide practice variation in use of ASMs clinically.

The objectives of this study were to (1) assess national trends in ASM prophylaxis in patients with acute brain injuries, (2) determine factors associated with higher ASM prophylaxis, and (3) perform an exploratory analysis of the association of ASM prophylaxis with discharge outcomes (in-hospital mortality and discharge to home).

Methods

We performed a retrospective cohort study using the PINC AI Healthcare Database (PHD) (formerly the Premier Healthcare Database). The PHD captures administrative, health care use, payor, and financial data from inpatient admissions at primarily nonprofit, nongovernmental, community, and teaching hospitals, with representation from hospitals in both rural and urban areas. It includes data on approximately 25% of annual inpatient admissions (up to 9 million/year) in the United States from more than 1,400 health care systems and hospitals [16–21]. The PHD is deidentified and Health Insurance Portability and Accountability Act (HIPAA)–compliant in accordance with the HIPAA Privacy Rule [22].

The PHD has been used in prior epidemiologic and comparative effectiveness studies [23–27]. We have previously used the PHD to describe national continuous electroencephalography (cEEG) use patterns for patients with cerebrovascular diseases [28]. The current study was approved by the Massachusetts General Brigham Institutional Review Board. Informed consent was not required for the analysis of this deidentified HIPAA-compliant database. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies [29].

Study Population

We identified adults (age ≥ 18 years at admission) who had an inpatient encounter during 2014–2022 with a primary *International Classification of Diseases* (ICD) diagnosis code for an acute brain injury: (1) 433–437 or I63 for ischemic stroke (IS), (2) 430–432 or I60–I62 for HS, or (3) 851–854 or S06 for TBI [30, 31]. The study population was restricted to those who survived and remained in inpatient care for at least 2 days. This restriction was applied to exclude patients with either severe or mild injuries who were deceased or discharged when first presenting to the emergency department or inpatient care. We included only the first episode of inpatient care for patients who had multiple admissions associated with an acute brain injury. The index date was set to be the second day of inpatient care (Supplemental Fig. 1). Indications for ASMs are not available in the dataset. Therefore, to exclude prevalent users of ASM or those receiving ASMs for secondary treatment of acute symptomatic seizures, we excluded (1) patients with ICD codes for epilepsy or seizures (see Supplemental Table 1), (2) patients who received any ASMs other than levetiracetam and phenytoin prior to and up to index date (i.e., days 0–2), and (3) patients who received levetiracetam or phenytoin on day 0.We excluded patients receiving levetiracetam and phenytoin on day 0 to exclude both prevalent users as well as patients who received single doses in the emergency department or initial hospital admission.

ASM Prophylaxis Definition

Supplemental Table 1 provides a full list of all the ASMs used in the cohort. We defined ASM prophylaxis based on use of levetiracetam or phenytoin. These two ASMS are the most routinely investigated and prescribed for primary prophylaxis and are not typically used for non-seizure indications [4–7]. The ASM prophylaxis cohort was defined as patients who received levetiracetam or phenytoin on the index date, whereas the non-ASM prophylaxis cohort was defined as those who did not receive any ASMs on the index date. Both prophylaxis and nonprophylaxis cohorts could have been exposed to levetiracetam or phenytoin prior to the index date (i.e., on day 1). We focused on the index date rather than presentation in the emergency department or the first day of inpatient care (day 0 or 1, respectively) to identify patients who maintained ASM prophylaxis while hospitalized beyond the day of admission. Henceforth, "ASM prophylaxis" refers to levetiracetam or phenytoin use on the index date (day 2).

Study Outcomes

The primary study outcome was time to mortality from the index date. This was recorded as a discrete variable based on the number of days from the index date (Supplemental Fig. 1). The secondary outcome was time to discharge to home from the index date, which was also recorded as a discrete variable. Other discharge

dispositions included home health, rehabilitation, skilled nursing facility, hospice, long-term acute care facility, or other facilities (together categorized as "Other discharge disposition"). Patients were followed for both outcomes until discharge from inpatient care and right censored at discharge. For the time to discharge to home outcome, mortality is regarded as a competing risk in the analyses.

Baseline Characteristics

Demographic data for each patient encounter included age, sex, race, and ethnicity. The Charlson Comorbidity Index was calculated based on diagnosis codes present on the day of admission [32, 33]. Use of mechanical ventilation, vasopressors, and anesthetics prior to the index date were recorded as markers of disease severity. Procedures including thrombectomy, craniectomies/craniotomies, and intracranial pressure monitoring, along with total number of procedures prior to index date, were also included as markers of neurologic and critical illness disease severity. Total number of procedures included all the distinct Current Procedural Terminology codes billed for prior to the index date. We recorded use of ASMs and benzodiazepines along with day of prescription. All medications were identified using PHD standard charge master codes. Hospital-level characteristics included geographic location, bed size, teaching versus nonteaching, and urban versus rural (see Supplemental Table 1 for a full list of diagnosis and procedure codes used in variable definitions).

Statistical Analyses

Separate analyses are presented for IS, HS, and TBI. We summarized the baseline characteristics in the overall, ASM prophylaxis, and non-ASM prophylaxis cohorts. The cumulative incidence of in-hospital mortality was estimated by ASM prophylaxis use using Kaplan–Meier curves, and the cumulative incidence of discharge to home among the cohorts was estimated using cumulative incidence functions.

Discrete time logistic hazard models were fit to assess associations between ASM prophylaxis on the index date and the hazard of mortality on an intent-to-treat basis [34, 35]. In unadjusted analyses, we fit models that included fixed effects for time (days) to model the baseline hazard along with a covariate for ASM prophylaxis use. In adjusted analyses, we expanded these models to adjust for baseline covariates, including age, sex, and race and ethnicity. The Charlson Comorbidity Index was used as a composite marker of comorbidities. We adjusted for variables that approximate the severity of injury and the baseline risk for seizures. These variables were measured prior to the index date and included use of mechanical ventilation, use of anesthetics, use of vasopressors, use of EEG monitoring, use of benzodiazepines, and use of levetiracetam or phenytoin prior to the index date. We also adjusted for hospital-level and provider-level variables, including hospital type, provider specialty, and payor type. For adjusted models among patients with HS, we also adjusted for the presence of cerebellar and subarachnoid hemorrhage. The full list of variables used in multivariable analysis are provided in Supplemental Tables 2 and 3. Cause-specific versions of these models were fit to assess associations between ASM use and the hazard of discharge to home [36].

Standard Protocol Approvals, Registrations, and Patients' Consent

The study was approved by the Massachusetts General Brigham Institutional Review Board. Informed consent was not required for the analysis of this deidentified HIPAA-compliant database.

Results

Baseline Characteristics

There were 739,213 patients who satisfied the inclusion and exclusion criteria (see Supplemental Fig. 2), including 568,254 patients with IS, 86,842 patients with HS, and 84,117 patients with TBI. Tables 1, 2 and 3 summarize the patient characteristics among those who received ASM prophylaxis versus those who did not across diagnostic categories. Among patients with IS, HS, and TBI, 10,959/568,254 (2%), 31,970/86,842 (37%), and 38,331/84,117 (46%) received ASM prophylaxis, respectively. Across all diagnostic categories, 95% of patients on ASM prophylaxis received levetiracetam and ~ 5% received phenytoin (detailed breakdown provided in Supplemental Table 4).

Across all diagnostic categories, patients in the ASM prophylaxis cohort were more likely to be younger, receive care at a teaching hospital, and receive care from critical care and neurology physicians. Patients in the ASM prophylaxis cohort were also more likely to require mechanical ventilation and receive anesthetics, vasopressors, and benzodiazepines prior to the index date. Neurosurgical procedures, including craniectomy/craniotomy and intracranial pressure monitoring prior to index date, were also more likely to be performed in patients receiving ASM prophylaxis. The ASM prophylaxis cohort across all diagnostic categories tended to have longer lengths of stay.

Associations with Mortality

Figure 1 shows the cumulative incidence curves for mortality across all three diagnostic categories, and Table 4 shows the unadjusted and adjusted hazard ratios (HRs) for mortality. Associations with ASM prophylaxis

Table 1 Baseline characteristics—ischemic stroke

Patient and admission characteristics	ASM prophylaxis ($n = 10,959$)	No ASM prophylaxis ($n = 557,295$)	*p*-value
Age, mean (SD)	68.74 (14.55)	70.59 (13.94)	< 0.001
Female, *n* (%)	5,479 (50.0)	278,713 (50.0)	0.981
Race, *n* (%)			< 0.001
Black	1,829 (16.7)	89,467 (16.1)	
Hispanic	825 (7.5)	35,973 (6.5)	
Other	791 (7.2)	31,622 (5.7)	
Unknown	580 (5.3)	24,270 (4.4)	
White	6,934 (63.3)	375,963 (67.5)	
Charlson Comorbidity Index, mean (SD)	2.87 (2.59)	2.91 (2.60)	0.077
Teaching hospital, *n* (%)	6,274 (57.2)	284,314 (51.0)	< 0.001
Urban hospital, *n* (%)	9,995 (91.2)	496,914 (89.2)	< 0.001
Admitting physician specialty, *n* (%)			
Critical care	734 (6.7)	14,475 (2.6)	< 0.001
Neurology	1,344 (12.3)	50,327 (9.0)	< 0.001
Other	8,881 (81.0)	492,493 (88.4)	< 0.001
Payor type, *n* (%)			
Medicare	7,028 (64.1)	370,380 (66.5)	< 0.001
Medicaid	1,353 (12.3)	48,336 (8.7)	< 0.001
Workers' compensation	10 (0.1)	470 (0.1)	0.936
Other managed care	1,393 (12.7)	72,695 (13.0)	0.312
Other government payor	168 (1.5)	8,182 (1.5)	0.604
Medication and procedure use prior to index, *n* (%)			
EEG monitoring	90 (0.8)	505 (0.1)	< 0.001
Mechanical ventilation	1,829 (16.7)	14,233 (2.6)	< 0.001
Thrombectomy	564 (5.1)	15,434 (2.8)	< 0.001
Craniectomy/craniotomy	26 (0.2)	21 (0.0)	< 0.001
Intracranial pressure monitoring	97 (0.9)	248 (0.0)	< 0.001
Total number of procedures, mean (SD)	4.55 (2.71)	3.68 (1.91)	< 0.001
Vasopressors	530 (4.8)	6,310 (1.1)	< 0.001
Anesthetics	2,571 (23.5)	37,053 (6.6)	< 0.001
Levetiracetam or phenytoin in day 1	6,022 (55.0)	1,762 (0.3)	< 0.001
Benzodiazepines	1,499 (13.7)	51,961 (9.3)	< 0.001
Discharge disposition, *n* (%)			
Mortality	1,916 (17.5)	21,046 (3.8)	< 0.001
Home discharge	1,658 (15.1)	189,665 (34.0)	< 0.001
Length of stay, mean (SD)	8.26 (6.90)	5.23 (4.51)	< 0.001

ASM Antiseizure medication, *EEG* Electroencephalogram, *SD* Standard deviation

exhibited heterogeneity across the diagnostic categories. In patients with IS, the cumulative incidence for mortality was higher in those receiving ASM prophylaxis. This is reflected in the unadjusted association analyses, in which patients in the ASM prophylaxis group were estimated to have a higher rate of mortality (HR 2.54, 95% confidence interval [CI] 2.42–2.67; Table 4). In the adjusted analyses, ASM prophylaxis continued to be associated with a higher rate of mortality (HR 2.02, 95% CI 1.89–2.16) after accounting for differences in baseline characteristics between those who received and did not receive ASM prophylaxis. Use of mechanical ventilation prior to index date was more common among patients with ASM prophylaxis and also exhibited strong adjusted associations with mortality (HR 3.30, 95% CI 3.15–3.45; Supplemental Table 2).

In patients with HS, ASM prophylaxis was associated with higher mortality rates in unadjusted analyses (HR 1.04, 95% CI 1.01–1.08). However, after adjustment, ASM prophylaxis was associated with lower rate of mortality

Table 2 Baseline characteristics—hemorrhagic stroke

Patient and admission characteristics	ASM prophylaxis ($n = 31,970$)	No ASM prophylaxis ($n = 54,872$)	*p*-value
Age, mean (SD)	63.36 (15.21)	67.34 (15.03)	< 0.001
Female, *n* (%)	16,750 (52.4)	26,702 (48.7)	< 0.001
Race, *n* (%)			< 0.001
Black	4,911 (15.4)	8,910 (16.2)	
Hispanic	3,304 (10.3)	4,843 (8.8)	
Other	2,691 (8.4)	3,395 (6.2)	
Unknown	2,413 (7.5)	4,296 (7.8)	
White	18,651 (58.3)	33,428 (60.9)	
Charlson Comorbidity Index, mean (SD)	2.87 (2.58)	2.92 (2.59)	0.005
Teaching hospital, *n* (%)	21,811 (68.2)	36,161 (65.9)	< 0.001
Urban hospital, *n* (%)	29,902 (93.5)	51,220 (93.3)	0.291
Admitting physician specialty, *n* (%)			
Critical care	3,912 (12.2)	5,379 (9.8)	< 0.001
Neurology	7,841 (24.5)	11,661 (21.3)	< 0.001
Other	20,217 (63.2)	37,832 (68.9)	< 0.001
Payor type, *n* (%)			
Medicare	15,434 (48.3)	31,700 (57.8)	< 0.001
Medicaid	4,810 (15.0)	6,582 (12.0)	< 0.001
Workers' compensation	35 (0.1)	73 (0.1)	0.395
Other managed care	6,559 (20.5)	8,363 (15.2)	< 0.001
Other government payor	513 (1.6)	804 (1.5)	0.111
Hemorrhage subtype, *n* (%)			
Cerebellar	881 (2.8)	4,774 (8.7)	< 0.001
Subarachnoid	11,894 (37.2)	8,856 (16.1)	< 0.001
Medication and procedure use prior to index date			
EEG monitoring	107 (0.3)	48 (0.1)	< 0.001
Mechanical ventilation	10,170 (31.8)	9,825 (17.9)	< 0.001
Thrombectomy	44 (0.1)	21 (0.0)	< 0.001
Craniectomy/craniotomy	29 (0.1)	10 (0.0)	< 0.001
Intracranial pressure monitoring	4,329 (13.5)	3,017 (5.5)	< 0.001
Number of procedures, mean (SD)	4.65 (3.06)	3.68 (2.56)	< 0.001
Vasopressors	1,678 (5.2)	1,620 (3.0)	< 0.001
Anesthetics	12,674 (39.6)	10,917 (19.9)	< 0.001
Levetiracetam or phenytoin on day 1	24,374 (76.2)	3,952 (7.2)	< 0.001
Benzodiazepines	2,354 (7.4)	4,023 (7.3)	0.874
Discharge disposition, *n* (%)			
Mortality	6,171 (19.3)	7,901 (14.4)	< 0.001
Home discharge	7,316 (22.9)	13,555 (24.7)	< 0.001
Length of stay, mean (SD)	11.43 (8.39)	8.15 (7.00)	< 0.001

ASM Antiseizure medication, *EEG* Electroencephalogram, *SD* Standard deviation

(HR 0.83, 95% CI 0.79–0.87). As with patients with IS, use of mechanical ventilation prior to the index date was more common among patients with ASM prophylaxis and exhibited strong adjusted associations with mortality (HR 7.667, 95% CI 7.28–8.058; Supplemental Table 2).

In patients with TBI, ASM prophylaxis was associated with mortality rates in unadjusted analysis (HR 1.07, 95% CI 1.00–1.14) but not in adjusted analysis (HR 0.97, 95% CI 0.89–1.06). Mechanical ventilation remained strongly associated with higher mortality rates (HR 1.95, 95% CI 1.76–2.16; Supplemental Table 2).

Associations with Discharge to Home

In contrast with the mortality associations, ASM prophylaxis exhibited similar associations with discharge to home across all the diagnostic categories.

Table 3 Baseline characteristics—traumatic brain injury

Patient and admission characteristics	ASM prophylaxis ($n = 38,331$)	No ASM prophylaxis ($n = 45,786$)	*p*-value
Age, mean (SD)	68.37 (18.98)	73.05 (17.15)	< 0.001
Female, *n* (%)	15,993 (41.7)	23,024 (50.3)	< 0.001
Race, *n* (%)			< 0.001
Black	2,845 (7.4)	2,992 (6.5)	
Hispanic	3,052 (8.0)	2,819 (6.2)	
Other	2,448 (6.4)	2,345 (5.1)	
Unknown	2,377 (6.2)	2,372 (5.2)	
White	27,609 (72.0)	35,258 (77.0)	
Charlson Comorbidity Index, mean (SD)	2.95 (2.61)	2.96 (2.58)	0.713
Teaching hospital, *n* (%)	27,215 (71.0)	26,883 (58.7)	< 0.001
Urban hospital, *n* (%)	35,759 (93.3)	42,244 (92.3)	< 0.001
Admitting physician specialty, *n* (%)			
Critical care	4,016 (10.5)	2,767 (6.0)	< 0.001
Neurology	4,425 (11.5)	3,749 (8.2)	< 0.001
Other	29,890 (78.0)	39,270 (85.8)	< 0.001
Payor type, *n* (%)			
Medicare	24,166 (63.0)	33,282 (72.7)	< 0.001
Medicaid	3,799 (9.9)	2,734 (6.0)	< 0.001
Workers' compensation	690 (1.8)	557 (1.2)	< 0.001
Other managed care	4,154 (10.8)	3,580 (7.8)	< 0.001
Other government payor	557 (1.5)	586 (1.3)	0.033
Medication/procedure use prior to index, *n* (%)			
EEG monitoring	53 (0.1)	15 (0.0)	< 0.001
Mechanical ventilation	4,187 (10.9)	1,767 (3.9)	< 0.001
Thrombectomy	1 (0.0)	2 (0.0)	1
Craniectomy/craniotomy	39 (0.1)	7 (0.0)	< 0.001
Intracranial pressure monitoring	747 (1.9)	141 (0.3)	< 0.001
Number of procedures, mean (SD)	3.74 (2.54)	3.12 (2.09)	< 0.001
Vasopressors	1,176 (3.1)	598 (1.3)	< 0.001
Anesthetics	7,882 (20.6)	3,805 (8.3)	< 0.001
Levetiracetam and phenytoin on day 1	29,414 (76.7)	2,126 (4.6)	< 0.001
Benzodiazepines	2,725 (7.1)	3,647 (8.0)	< 0.001
Discharge disposition, *n* (%)			
Mortality	2364 (6.2)	1,850 (4.0)	< 0.001
Home discharge	12,778 (33.3)	16,236 (35.5)	< 0.001
Length of stay, mean (SD)	7.16 (6.52)	5.32 (4.82)	< 0.001

ASM Antiseizure medication, *EEG* Electroencephalogram, *SD* Standard deviation

The cumulative incidence of discharge to home was consistently lower in those receiving ASM prophylaxis (Fig. 2). Adjusted estimates from Table 4 also indicate that ASM prophylaxis was associated with lower rates of discharge to home across all three diagnostic categories (HR 0.40, 95% CI 0.37–0.42 in IS; HR 0.61, 95% CI 0.58–0.64 in HS; and HR 0.69, 95% CI 0.68–0.72 in TBI).

Discussion

Antiseizure medication prophylaxis varies by etiology of brain injury, and there remains practice variation within diagnostic categories. In our cohort, up to half of patients with TBI received prophylaxis, followed by 38% of patients with HS. Only 2% of patients with IS received prophylaxis. Risk for acute symptomatic seizures is higher in patients with TBIs (2–15%) and HS (10–18%)

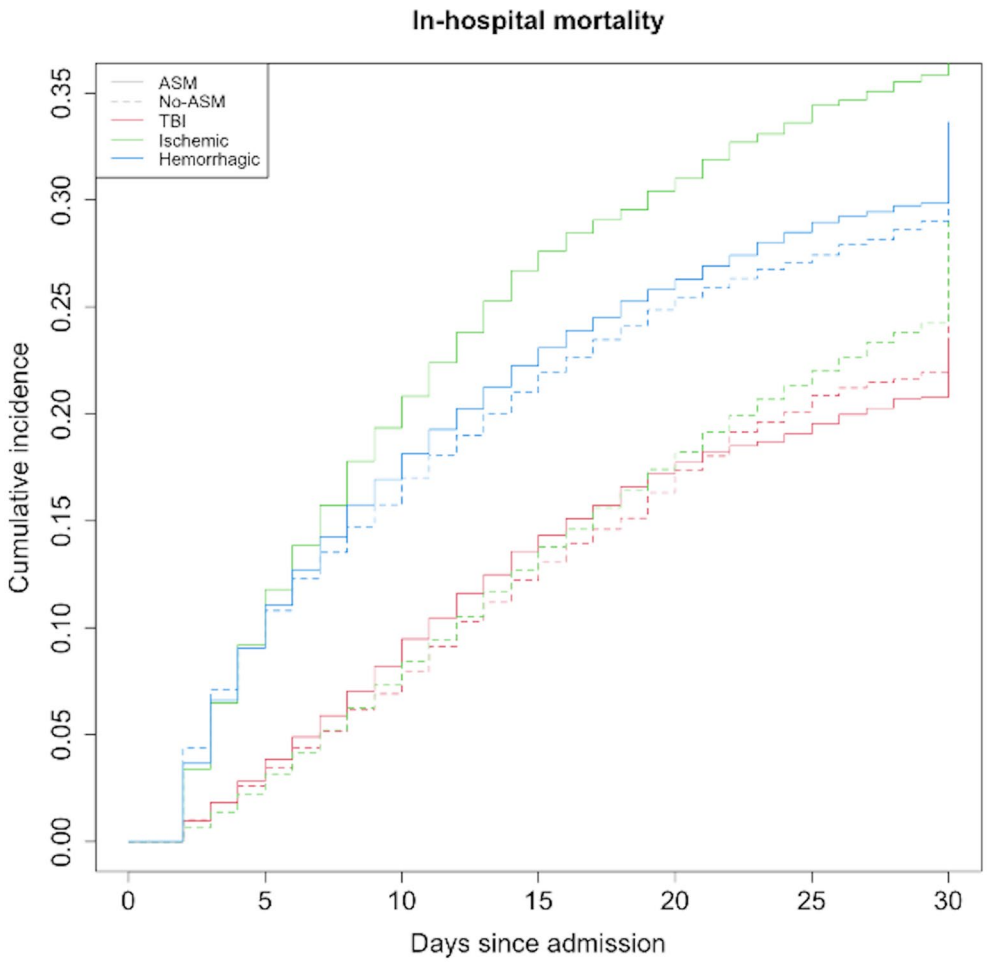

Fig. 1 Cumulative incidence curves for mortality. Cumulative incidence of mortality among ASM prophylaxis and control cohorts in ischemic stroke, hemorrhagic stroke, and TBI. ASM, antiseizure medication, TBI, traumatic brain injury

Table 4 Associations between ASM prophylaxis and hazard of mortality and discharge to home

	Unadjusted			Adjusted[a]		
	ASM prophylaxis, HR[b]	95% CI	*p* value	ASM prophylaxis, HR[b]	95% CI	*P* value
Mortality						
Ischemic stroke	2.54	2.42–2.67	< 0.001	2.02	1.89–2.16	< 0.001
Hemorrhagic stroke	1.04	1.01–1.08	0.024	0.83	0.79–0.87	< 0.001
Traumatic brain injury	1.07	1–1.14	0.039	0.97	0.89–1.06	0.535
Discharge to home						
Ischemic stroke	0.32	0.31–0.34	< 0.001	0.4	0.37–0.42	< 0.001
Hemorrhagic stroke	0.68	0.66–0.7	< 0.001	0.61	0.58–0.64	< 0.001
Traumatic brain injury	0.77	0.75–0.79	< 0.001	0.69	0.67–0.72	< 0.001

Cause-specific versions of these models were fit to assess associations between ASM prophylaxis and the hazard of discharge to home. *ASM* Antiseizure medication, *CI* Confidence interval, *HR* Hazard ratio

[a] In adjusted analyses, the models were additionally adjusted for baseline covariates that approximate the severity of injury and the baseline risk for seizures

[b] "ASM prophylaxis HR" refers to hazard ratio for prophylaxis on day 2 of admission in discrete-time logistic hazard models that includes fixed effects for time and an indicator for being in the prophylaxis cohort

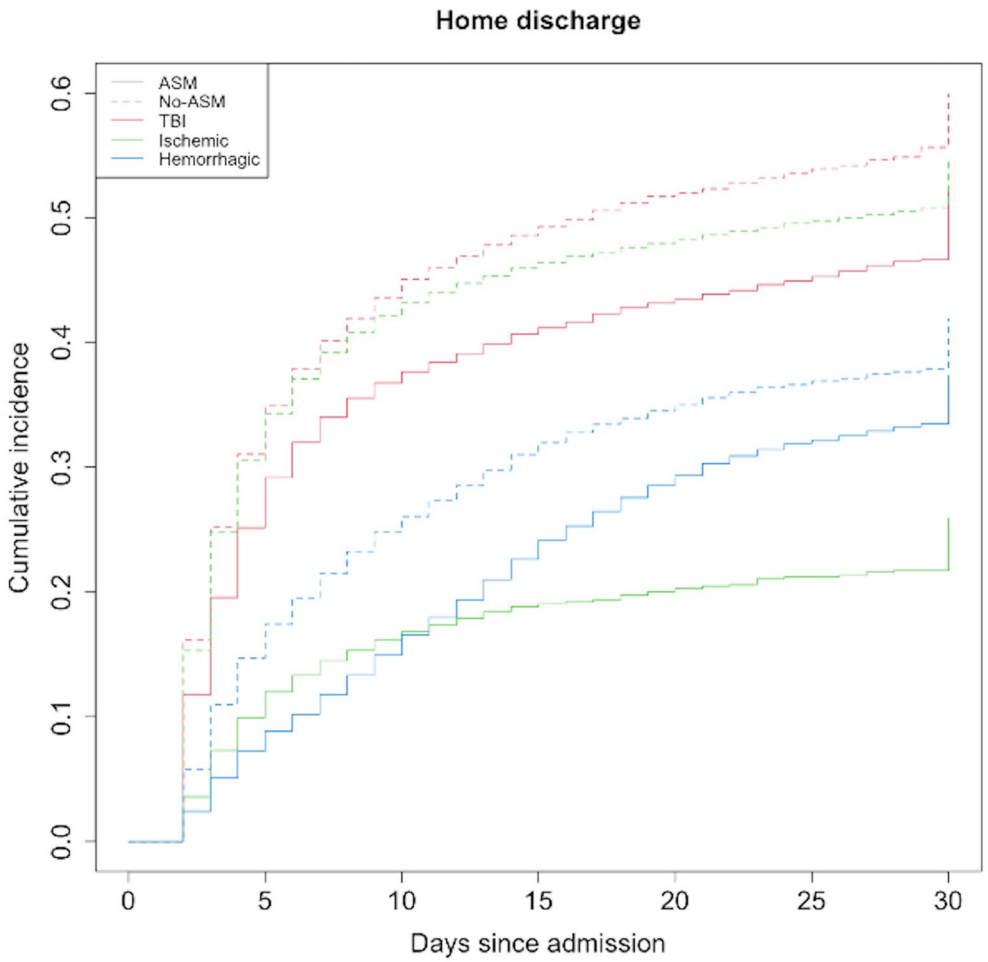

Fig. 2 Cumulative incidence curves for discharge to home. Cumulative incidence of discharge to home among an ASM prophylaxis and control cohorts in ischemic stroke, hemorrhagic stroke, and TBI. ASM, antiseizure medication, TBI, traumatic brain injury

compared with patients with IS (3–6%) [1]. These observations in our study sample are also consistent with consensus guidelines, which provide weak recommendations for brief seizure prophylaxis in patients with TBI and subarachnoid hemorrhage [6, 7] and recommend against primary seizure prophylaxis for patients with IS [5].

Across all diagnostic categories, patients with more severe illness, as evidenced by the need for mechanical ventilation, were more likely to receive ASM prophylaxis. Other markers of illness severity, including admission to critical care and use of anesthetics and vasopressors, were also more frequent among patients receiving ASM prophylaxis. This suggests illness severity may be a driver for decisions around use of ASM prophylaxis. One potential explanation is that acute symptomatic seizures are more frequent in more severe brain injuries, and, therefore, ASM prophylaxis may be used more frequently in such patients. A negligible portion of patients underwent cEEG monitoring across all diagnostic categories. Prior work from national data sources shows that less than 2% of patients with brain injuries undergo cEEG monitoring [28]. There are likely fewer patients with cEEG monitoring in this study, as patients with ICD codes for seizures and prevalent ASM users were excluded.

In our analysis of associations with outcomes, ASM prophylaxis had heterogenous associations with mortality across disease categories. ASM use was associated with a lower hazard of mortality in and patients with TBI and HS but with a higher hazard of mortality in patients with IS. The primary drivers of these associations are likely unobserved factors pertinent to the underlying etiology, illness severity, and associated interventions, as reflected by the strong associations between ASM use and outcomes with related observed factors, including vasopressors, mechanical ventilation, and anesthetics. Although we adjust for use of these procedures and medications that serve as approximate markers for these underlying factors, there likely remains unmeasured

residual confounding that continued to influence the adjusted results. Patients with HS and TBI also have a higher risk for seizures compared with patients with IS, which may also explain the differential association with ASM prophylaxis and mortality.

ASM prophylaxis was associated with a lower hazard for discharge to home across all diagnostic categories. This may also reflect confounding by the underlying illness severity as with mortality. For example, use of ASM prophylaxis may coincide with other acute care in patients with greater illness severity that increases survival but predisposes patients to longer lengths of stay, increased morbidity, and discharge to other health care facilities. Use of mechanical ventilation, vasopressors, anesthetics, and benzodiazepines was a significant predictor of both mortality and discharge disposition, highlighting the role of illness severity. The independent associations of ASM prophylaxis with mortality and with discharge disposition thus warrant further evaluation through large, randomized studies.

There were several limitations of this study. This is a retrospective study in which the study population was identified based on ICD codes. These codes are subject to error, and the population of patients with acute brain injury may not have been captured with full accuracy. Moreover, data on the indications for ASM use were not available. We aimed to assess associations with ASM used for primary prophylaxis and therefore excluded patients with seizures or epilepsy diagnosis codes along with potential prevalent users of ASMs. Nevertheless, there may remain some prevalent users or patients with acute symptomatic seizures in our cohort because of inaccuracies in the codes. Although indications for anesthetics and vasopressors are not available, we have included invasive surgical procedures, including craniectomies/craniotomies, thrombectomy, total number of procedures, and mechanical ventilation, to capture both disease severity and potential indications for anesthetic and vasopressor use. The dataset does not capture data on clinical disease severity scores, including neurologic injury severity scores, such as the Glasgow Coma Scale, National Institutes of Health Stroke Scale, and intracerebral hemorrhage scores. For exploratory outcome analysis, although we adjusted for surrogate markers of injury severity, such as the use of other medications and procedures, some degree of unmeasured confounding may remain. The confounding bias may be higher in IS, in which ASMs are less commonly used, as compared with TBI and HS populations. In TBI and HS, prophylaxis is more common, and, therefore, the preliminary estimates are less likely to be impacted by strong confounding bias. Finally, we examined short-term outcomes of discharge mortality and discharge to home. Future studies are needed to examine long-term outcomes beyond those captured during hospitalization.

Conclusions

In this large-scale, up-to-date investigation of ASM prophylaxis patterns in real-world clinical practice, we found ASM prophylaxis is commonly used in patients with acute brain injuries. Patients with TBI and HS are more likely to have received prophylaxis compared with patients with IS. We identified patient characteristics (i.e., disease type and illness severity) as well as hospital/admission characteristics (e.g., teaching hospital, admitting specialty) that are associated with greater propensity for ASM use. ASM prophylaxis use exhibited independent associations with mortality and discharge to home. Further comparative studies are needed to determine which specific patients benefit from ASM treatment and to guide appropriate indications, timing, dosing, and duration of treatment.

Supplementary Information

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Author Contributions

DC contributed to the design of the work, analysis and interpretation of data, and drafting the manuscript. MBF contributed to analysis and interpretation of data and reviewing the manuscript for important intellectual content. MBW contributed to design of the work, interpretation of data, and reviewing the manuscript for important intellectual content. LM contributed to design of the work, interpretation of data, and reviewing the manuscript for important intellectual content. SFZ contributed to conception and design of the work, acquisition, analysis and interpretation of the data, and drafting the manuscript. All others approved the final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data Availability

Upon reasonable request and institutional approval, deidentified data that support our findings could be available for reviewers.

Declarations

Conflict of interest

S.F.Z. is supported by funding from the National Institutes of Health (NIH) K23NS114201, R01NS131347, R01AG082693, R01NS126282. S.F.Z. is a clinical neurophysiologist for Corticare and has received speaker honoraria from Marinus and royalties from Springer, all unrelated to this work. L.M. is supported by funding from the NIH (1K08AG053380-01A1, 1R01AG062282-01) and the Epilepsy Foundation (Epilepsy Learning Healthcare System) and is the director of the Data Coordinating Center. M.B.W. is supported by the Glenn Foundation for Medical Research and American Federation for Aging Research

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Ethical approval
This article is in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting checklist. The article has not been published elsewhere and is not under consideration by another journal. The retrospective study adheres to ethical guidelines and was approved by the Massachusetts General Brigham Institutional Review Board.

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