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Real-world continuous EEG utilization and outcomes in hospitalized patients with acute cerebrovascular diseases

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Abstract

Background: Continuous Electroencephalography (cEEG) is recommended for hospitalized patients with cerebrovascular diseases and suspected seizures or unexplained neurological decline. We sought to 1) to identify areas of practice variation in cEEG utilization, 2) determine predictors of cEEG utilization, 3) evaluate whether cEEG utilization is associated with outcomes in patients with cerebrovascular diseases.

Methods: This cohort study of the Premier Healthcare Database (2014–2020), included hospitalized patients age ≥18 years with cerebrovascular diseases (identified by ICD codes). cEEG was identified by ICD/CPT codes. Multivariable lasso logistic regression was used to identify predictors of cEEG utilization and in-hospital mortality. Propensity score-matched analysis was performed to determine the relation between cEEG use and mortality.

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Potential conflicts of interest
Dr. Amerineni is a data scientist for CertainTeed unrelated to this work. Dr. Zafar is a clinical neurophysiologist for Corticare, unrelated to this work.
Dr. Westover is cofounder of Beacon Biosignals unrelated to this work.

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Results: 1,179,471 admissions were included;16,777 (1.4%) underwent cEEG. Total number of cEEGs increased by 364% over 5 years (average 32%/year). On multivariable analysis, top five predictors of cEEG use included seizure diagnosis, hospitals with >500 beds, regions Northeast and South, and anesthetic use. Top predictors of mortality included use of mechanical ventilation, vasopressors, anesthetics, anti-seizure medications and age. Propensity analysis showed cEEG was associated with lower in-hospital mortality (Average Treatment Effect −0.015 [CI −0.028−−0.003], Odds ratio 0.746 [CI 0.618–0.900].

Conclusions: There has been a national increase in cEEG utilization for hospitalized patients with cerebrovascular diseases, with practice variation. cEEG utilization was associated with lower in-hospital mortality. Larger comparative studies of cEEG-guided treatments are indicated to inform best practices, guide policy changes for increased access, and create guidelines on triaging and transferring patients to centers with cEEG capability.

Keywords

continuous EEG; health services research; machine learning; cerebrovascular diseases; outcomes

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Introduction

Electrographic epileptiform abnormalities (including seizures, periodic and rhythmic patterns) can be seen in up to 40% of patients with acute cerebrovascular diseases.[1–4] In patients with cerebrovascular diseases, these epileptiform abnormalities (EA) are associated with increased metabolic stress, reductions in brain tissue oxygenation, cerebral edema and secondary brain injury.[5–8] EA also increase the risk of mortality and poor functional outcomes.[9.10] In particular, increasing quantitative burden of EA directly results in increased probability of mortality and poor functional outcomes.[9–10] Consensus guidelines, therefore, recommend continuous Electroencephalography (cEEG) in hospitalized patients with acute cerebrovascular diseases and concern for subclinical seizures.[11] Other indications for cEEG include assessment of response to anti-seizure therapy in patients with status epilepticus, monitoring depth of sedation, and characterization of paroxysmal events. In patients with aneurysmal subarachnoid hemorrhage, cEEG use is also suggested for ischemia monitoring.[11] Development of EA, increasing burden of EA, and development of focal slowing are harbingers delayed cerebral ischemia.[12] Despite evidence that EA can worsen outcomes, and published recommendations on indications for cEEG monitoring, there is limited and conflicting data on whether cEEG guided clinical care and treatment (including anti-seizure treatment) improves patient outcomes.[9,13–17]

In this study we define national cEEG utilization patterns in patients with acute cerebrovascular diseases. The primary objectives were 1) to identify areas of practice variation in cEEG utilization, 2) determine predictors of cEEG utilization, 3) evaluate whether differences in cEEG utilization are associated with outcomes (in-hospital mortality). Ultimately, we generate evidence for future rigorous comparative effectiveness studies of cEEG guided treatment.

Methods

We performed a retrospective cohort study using the Premier Healthcare Database (PHD) (January 2014-April 2020). The PHD includes administrative, healthcare utilization, and billing data from approximately 25% of annual inpatient discharges (up to 8 million/year) from hospitals and healthcare systems across the United States.[18–22] The database is comprised primarily of non-profit, nongovernmental, community and teaching hospitals, and medical systems from both rural and urban areas. All information in the PHD is de-identified and HIPAA-compliant in accordance with the HIPAA Privacy Rule.[23]

The PHD contains hospital level data including hospital location (US region) size, teaching vs. non-teaching status, rural vs. urban setting. Patient level data include demographics, admission and discharge diagnosis, admission type (e.g., elective vs. urgent vs. emergent), discharge disposition and discharge health status. Provider level data include admitting and attending physician specialties, and diagnostic procedure ordering provider specialty. Billed services include medications and devices, laboratory tests performed, diagnostic and therapeutic services, and microbiology tests. Date-stamped logs are available for all billed items including medications and diagnostic procedures. The PHD contains healthcare payor data, and data from all patients admitted at the participating hospitals are included independent of payor status. The database is updated weekly, with less than 1% missing data for most data elements, and less than 0.01% missing data for key data variables such as demographic and diagnostic information.[18]

The PHD has been used in prior epidemiologic and comparative effectiveness studies.[24–28] We used the Premier database to describe national cEEG utilization patterns between January 2014 and April 2020. The study was approved by the Massachusetts General Brigham Institutional Review Board. Informed consent was not required for the analysis of this de-identified HIPAA compliant database. The results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.[29]

Patient population: Cerebrovascular disease cohort

Adult patients (age ≥18 years) with cerebrovascular disease were identified using admission, primary and secondary diagnosis ICD 9 and 10 codes: 430–437 and I60–168.[30] We excluded elective admissions from home to remove patients potentially admitted to the Epilepsy Monitoring Unit. Figure 1. Displays the inclusion and exclusion flow chart.

Clinical variables and outcomes

For each patient encounter, we collected demographic variables including age, gender, and ethnicity, clinical variables including concomitant seizure diagnosis as defined by admission, primary and secondary ICD 9 and 10 codes (supplemental table 1), use of mechanical ventilation, vasopressors, anti-seizure medications and anesthetics. Charlson Comorbidity Index (CCI) was calculated as an integrated measure of patient comorbidities.[31,32] Hospital level data included geographic location, bed size, teaching vs. non-teaching, urban vs. rural, volume of cEEGs performed per year, and volume of cerebrovascular disease patients admitted per year. Additional administrative information included payor type, admitting, and treating physician specialties.

CPT (95720, 95951, 95717, 95718, 95956, 95719) and ICD 9 and 10 (89.19, 4A10X4Z) procedure codes were used for identification of cEEG.[16,17,33] ICD 9 and 10 cEEG codes were used to identify the day of procedure. cEEG ordering provider specialties were also recorded.

Statistical analysis

Prediction models—Frequencies, mean, median, and inter-quartile ranges were calculated for descriptive analysis. Multivariable analysis was performed using lasso logistic regression to 1) identify predictors of cEEG utilization at any time point during hospitalization, 2) determine predictors of in-hospital mortality. The lasso model was selected for the analysis as it performs automatic covariate selection and can reduce both multi-collinearity and model over-fitting. The full list of clinical variables used in the multivariable models are provided in supplemental Table 2. We included baseline clinical variables including seizure and stroke diagnosis present on admission (ICD codes present on admission flag), and Charlson comorbidity score. Measures of disease severity included use of mechanical ventilation, vasopressors, and anesthetics on admission. All clinical variables were measured at the time of hospital admission, and prior to cEEG initiation. Hospital level data included hospital size, location, teaching vs. non-teaching, and cEEG volume. Provider level data included admitting and attending physician specialty.

We performed nested 10-fold stratified cross validation (CV) for hyperparameter tuning and model validation. Stratified CV was used to maintain the same class ratio as the original dataset through all folds. The data was split into 10 groups. For each fold of outer CV, one group was selected as a testing set and the rest were used as training sets. We performed grid search based hyper-parameter tuning using 10-fold inner CV on the outer CV training data. We used class weights parameter to address class imbalance. The optimal hyper-parameters were selected using the maximum mean area under the receiver operating curve (AUROC) obtained by averaging the values from inner testing sets. The lasso model was trained using the optimal hyperparameters on the outer CV training data. The AUROC was used to evaluate the model on the outer CV test set. Ten different lasso models were trained and the best hyperparameters were selected by averaging the mean AUROC over the 10-fold nested CV. Final model performance was assessed using the AUROC.

Propensity score-matched analysis of cEEG—A propensity score matched analysis was performed to determine the relationship between cEEG use and in-hospital mortality. The propensity score regression models included all variables that were predictors of cEEG use and of in-hospital mortality, and were measured at the time of admission, prior to exposure to cEEG. Details of propensity score calculation and matching and full list of predictors is shown in supplemental Table 3. We performed 1:1 nearest neighbor greedy matching with replacement. The covariate balance between patient encounters undergoing cEEG vs. not was assessed using standardized mean differences before and after matching. We considered an absolute standardized mean difference <0.1 as sufficient level of balance.

Tolerance for overlap assumption was set as 1E-5. We estimated the average treatment effect (ATE) and odds ratio (OR) with their 95% confidence interval (CI) for in-hospital mortality.

Results

1,179,471 patient encounters met inclusion criteria for cerebrovascular diseases, and 16,777 (1.4%) underwent cEEG monitoring as defined by ICD and CPT codes. Table 1. summarizes the clinical, demographic and geographical variables. Urban, teaching, and larger hospitals were more likely to perform cEEG monitoring. Admissions with higher illness severity as measured by the CCI, use of vasopressors and mechanical ventilation were more likely to undergo cEEG. Admissions to neurology specialists or admitted with admission diagnosis of seizures were also more likely to undergo cEEG. With regards to geographic regions, patients admitted with cerebrovascular diseases in the South and Northeast were most likely to undergo cEEG monitoring.

Table 2. shows the number of cEEGs performed per year between 2014–2020. The total number of cEEGs performed in patients with cerebrovascular diseases increased by 364% over 5 years (excluding 2020, as only data for the first quarter were available), and on average by 32% per year. There was a 1.7-fold increase in the total number of hospitals using cEEG between 2014–2019.

Supplemental Table 4. shows the timing of cEEG from admission. Majority of cEEGs were performed within the first 7 days, with approximately half performed within the first 2 days of admission. Patients were more likely to undergo cEEG if the cerebrovascular disease diagnosis was a primary diagnosis, and if the diagnosis had a present on admission flag. Supplemental Table 5 shows the clinical and demographic characteristics and cEEG utilization patterns across patients with ICD codes for ischemic stroke vs. hemorrhagic stroke. Patient encounters in urban, academic, and larger hospitals, and those with higher illness severity as measured by the CCI, use of vasopressors and mechanical ventilation were more likely to undergo cEEG, regardless of cerebrovascular disease subtype.

Predictors of cEEG utilization.

Predictors of cEEG utilization their regression coefficients are shown in Figure 2. The top predictors in the model were seizure “present on admission” flag, admissions in the Northeast, and admissions to larger hospitals (> 500 beds). Use of anti-seizure medications and anesthetics on day of admission were also selected among predictors of cEEG use. The model had on AUROC of 0.739 (Confidence Interval (CI) 0.738–0.739) in the test set.

Predictors of in-hospital mortality.

Figure 3 shows predictors of in-hospital mortality across the cohort. The top predictors in the model were use of mechanical ventilation and vasopressor on the day of admission and age. Anti-seizure medications on day of admission were selected among predictors of mortality. cEEG use was identified as a predictor, with a negative coefficient for in-hospital mortality (i.e. in the model use of cEEG was associated with a lower probability of in-hospital mortality). The model had on AUROC of 0.864 (CI 0.863–0.864) in the test set.

Association of cEEG use with in-hospital mortality – propensity matched analysis.

Covariate balance and propensity score overlap after matching are shown in supplemental Table 3 and supplemental Figure 1. All patient encounters that underwent cEEG were propensity-score matched to controls with no cEEG (the mean nearest neighbor distance (difference between propensity scores) was 0.00003). After adjusting for the propensity score, we found that cEEG use was associated with lower in-hospital mortality- ATE −0.015 [CI −0.028- −0.003], p=0.0195, OR 0.746 [CI 0.618–0.900], p=0.0025.

Discussion

There has been a national increase in the use of cEEG for patients admitted with cerebrovascular diseases. cEEG utilization varies with geographic regions, hospital type, admitting and attending provider specialties, and across race and ethnicities. Higher illness severity as supported by the use of mechanical ventilation, anesthetics and vasopressors were also selected among predictors of cEEG utilization. With regards to hospital outcomes, cEEG utilization was associated with lower in-hospital mortality.

We identified differences in cEEG utilization by geographic regions, with the Northeast being selected among the top predictors, followed by the South. Prior studies on cEEG utilization in heterogenous populations have shown similar distribution, with the Northeast being a predictor of cEEG use.[16,17] Other predictors included larger, teaching hospitals, and centers located in urban areas. Similar disparities have been demonstrated in access to other aspects of acute stroke care between metropolitan and non-metropolitan regions and highlight the need for guidelines and policy changes to increase access to neurological services.[34]

White patients were more likely to undergo cEEG compared with Blacks. Racial disparities have been demonstrated in stroke care and outcomes across the United States.[34] These differences may be attributed to both patient level factors, and potential healthcare systems characteristics. For example, the racial differences may be a reflection of the primary populations seen in healthcare systems most likely to perform cEEG.

With regards to timing of cEEG, majority of cEEGs were performed early (during the first 48 hours of admission). Patients with acute stroke as a secondary diagnosis were more likely to receive cEEG later during hospitalization (after 7 days). This may be the result of strokes being in-hospital events and cEEG being performed due to changes in neurologic status later in the hospital course.

cEEG utilization was associated with lower in-hospital mortality. Two prior studies out of the Nationwide Inpatient Sample have similarly shown that cEEG utilization is associated with lower in-hospital mortality in heterogenous cohorts of hospitalized patients on mechanical ventilation.[16,17] We hypothesize our findings, along with findings from prior studies, suggest a potential benefit of cEEG monitoring in patients with acute cerebrovascular diseases, and propose larger comparative effectiveness studies of cEEG monitoring and cEEG-guided treatments in this population.

While cEEG use has increased overall, our study highlights persistent practice variation – with lower use in non-urban and non-teaching hospitals. Given the lack of cEEG availability in certain areas, understanding the true impact of monitoring and treatment of subsequent findings is critical to understand and inform best practices, and ensure policy changes for increased access. Determining which patients benefit most from cEEG guided care will also enable development of guidelines on triaging and transferring patients to centers with cEEG capability.

While randomized trials would be considered the gold standard to determine the effectiveness of cEEG guided treatment, they may not be reflective of the real world setting, with additional limitations in the critical care setting including recruitment decisions and windows overlapping with the dynamic high acuity clinical period, barriers to consent, and recruitment of racial/ethnic minorities.[35–38] Other barriers to designing a feasible randomized trial of cEEG guided anti-seizure treatment include the clinical heterogeneity of cerebrovascular diseases, and logistical challenges in administration of interventions within the window where benefit is possible, particularly in light of the differential availability of cEEG across hospitals.[35,38] Our study demonstrates real-world practice variation that can potentially be leveraged to exploit natural experiments and provide valuable insights and a path forward towards determining the comparative effectiveness and cost effectiveness of cEEG utilization and cEEG guided treatments. Such comparative effectiveness research combining large observational data and causal inference methods that emulates a target randomized trial, have been used to examine treatment strategies, for anemia, HIV and prostate cancer.[39–42]

Limitations of our study include the use of ICD and procedure codes that may not completely identify our cohort of interest, as is the case with many studies using administrative datasets. Additionally, while we reviewed cEEG utilization, we did not analyze post cEEG treatment decisions e.g., initiation or escalation of anti-seizure treatments, that are likely to be the key drivers of outcome rather than the diagnostic procedure itself. We did not have complete data for the year 2020 and have not captured the COVID 19 pandemic in our study. There were reductions in cEEG utilization in certain centers and regions across the United States during the pandemic[43], and while future studies are indicated to determine the clinical impact and implications of the changes in cEEG utilization during the pandemic, this is beyond the scope of the current study. Finally, we only examined cEEG utilization and did not evaluate use of brief or routine EEGs. Certainly centers that do not have access to cEEG may have access to shorter routine EEGs, and future studies are indicated to compare routine vs. cEEG guided treatment in patients with acute cerebrovascular diseases.

Conclusion

Although there has been a national increase in cEEG utilization for patients with cerebrovascular diseases, there continues to be practice variation across hospitals and provider types. We found that cEEG use was associated with lower in-hospital mortality. Large comparative effectiveness studies are needed to determine the impact of cEEG guided treatment on outcomes and inform policies and guidelines on access to cEEG. Linkage of multi-center electronic health records, administrative and EEG datasets, can enable exploitation of natural experiments leveraging practice variation and using advanced causal inference methods and significantly advance our knowledge on indications and impact of cEEG guided anti-seizure treatment and pave the path forward for complimentary practical and feasible randomized trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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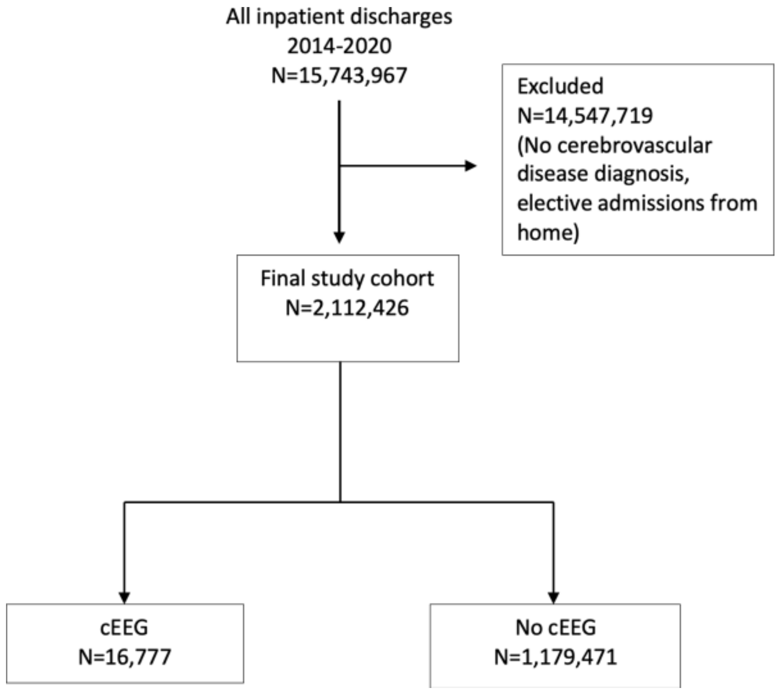

Figure 1: Inclusion and Exclusion Flow Chart

The inclusion and exclusion flow chart is shown. cEEG: Continuous electroencephalography

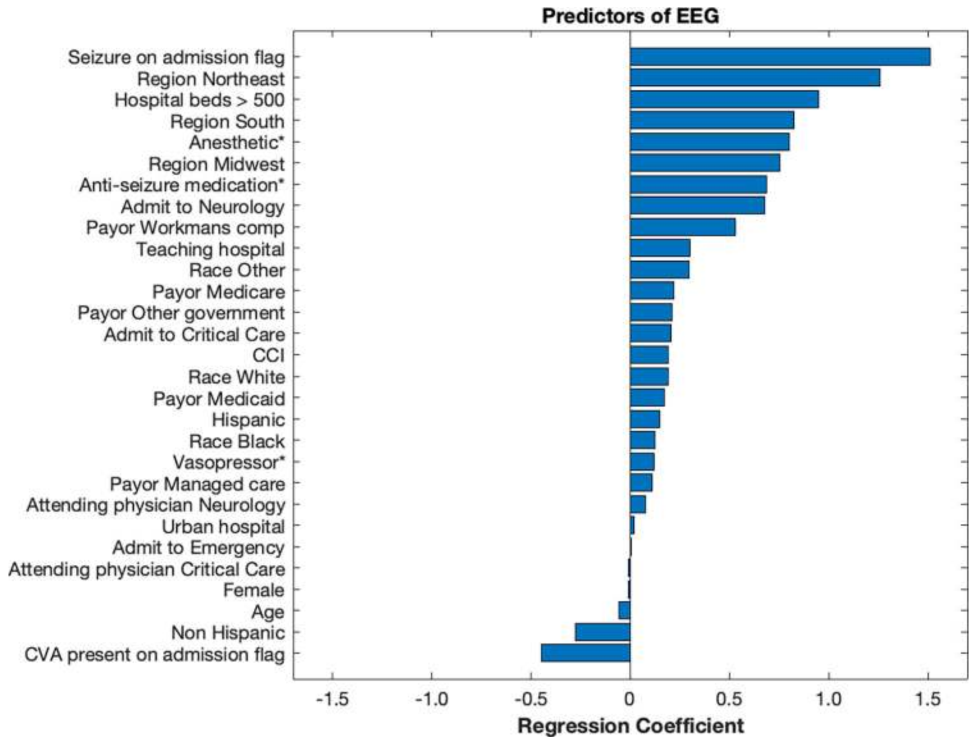

Figure 2: Predictors of cEEG

Predictors of cEEG and their regression coefficients are shown. EEG: electroencephalography; CVA: Cerebrovascular accident * Medications prescribed on day 0–1 of admission

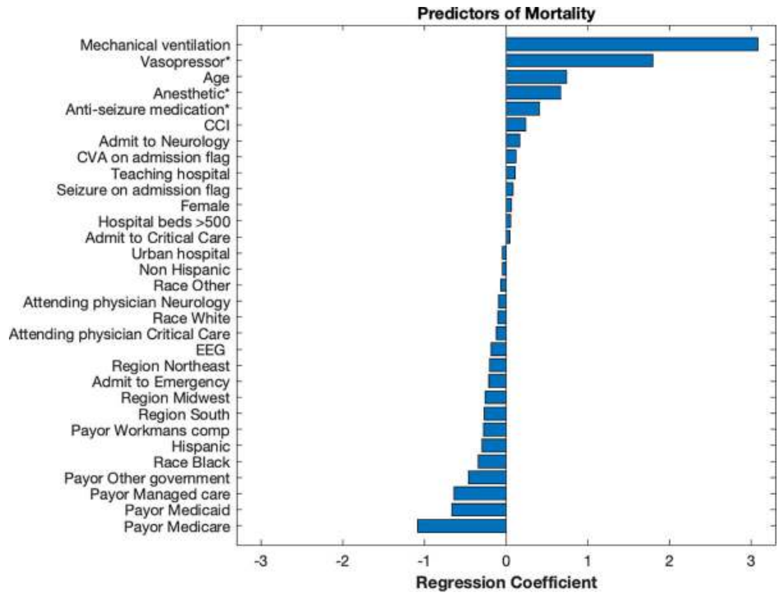

Figure 3: Predictors of In-hospital Mortality

Predictors of in-hospital mortality and their regression coefficients are shown. CCI: Charlson Comorbidity Index; EEG: elecroencephalography * Medications prescribed on day 0–1 of admission

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Table 1.

Clinical and Demographic Variables

	EEG (N= 16,777)	No EEG (N= 1,179,471)	P value
Age groups			
[18.0, 40.0)	877 (5.2%)	34,496 (2.9%)	<0.0001
[40.0, 50.0)	1,168 (7.0%)	71,089 (6.0%)	
[50.0, 60.0)	2,677 (16.0%)	173,919 (14.7%)	
[60.0, 70.0)	4,028 (24.0%)	267,055 (22.6%)	
[70.0, 80.0)	4,338 (25.9%)	294,739 (25.0%)	
[80.0, 90.0)	3,689 (22.0%)	338,173 (28.7%)	
Sex, female	8,257 (49.3%)	594,639 (50.4%)	0.002
Race			
White	11,462 (68.3%)	857,372 (72.7%)	<0.0001
Black	2,701 (16.1%)	175,483 (14.9%)	
Other	2,286 (13.6%)	124,170 (10.5%)	
Unknown	328 (2.0%)	22,446 (1.9%)	
Ethnicity			
Hispanic	1,558 (9.3%)	70,147 (5.9%)	<0.0001
Non-Hispanic	10,735 (64.0%)	867,092 (73.5%)	
Unknown	4,484 (26.7%)	242,232 (20.5%)	
Urban hospital	15,239 (90.8%)	1,050,350 (89.1%)	<0.0001
Rural hospital	1,538 (9.2%)	129,121 (10.9%)	
Teaching/Academic hospital	12646 (75.4%)	602,554 (51.1%)	<0.0001
Hospital bed size			
000–099	113 (0.7%)	37,885 (3.2%)	<0.0001
100–199	549 (3.3%)	124,508 (10.5%)	
200–299	1,378 (8.2%)	179,402 (15.2%)	
300–399	1,152 (6.8%)	185,265 (15.7%)	
400–499	1,442 (8.6%)	167,885 (14.2%)	
500+	12,143 (72.4%)	484,526 (41.1%)	
Northeast	4792 (28.6%)	188,201 (16.0%)	<0.0001
Urban	3,616 (75.5%)	174,006 (92.5%)	
Rural	1,176 (24.5%)	14,195 (7.5%)	
Academic	4,550 (94.9%)	146,084 (12.4%)	
Midwest	2985 (17.8%)	252,501 (21.4%)	<0.0001
Urban	2,979 (99.8%)	229,781 (91.0%)	
Rural	6 (0.2%)	22,720 (9.0%)	

	EEG (N= 16,777)	No EEG (N= 1,179,471)	P value
Academic	2,662 (89.2%)	161,896 (64.1%)	
West (%)	950 (5.7%)	179,112 (15.2%)	<0.0001
Urban	932 (98.1%)	160,953 (89.9%)	
Rural	18 (1.9%)	18,159 (9.1%)	
Academic	618 (65.1%)	54,279 (30.3%)	
South (%)	8050 (48.0%)	559,657 (47.4%)	0.17
Urban	7,712 (95.8%)	485,610 (86.8%)	
Rural	338 (4.2%)	74,047 (13.2%)	
Academic	4,816 (59.8%)	240,295 (42.9%)	
Admitting physician specialty			<0.0001
Neurology/Neurosurgery	4295 (25.6%)	115,602 (9.8%)	
Medical and Surgical critical care	4282 (25.5%)	344,861 (29.2%)	
Other	8200 (48.9%)	719,008 (61.0%)	
Attending physician specialty			<0.0001
Neurology/Neurosurgery	4343 (25.9%)	126,088 (10.7%)	
Medical and Surgical critical care	4897 (29.2%)	384,636 (32.6%)	
Other	7537 (44.9%)	668,747 (56.7%)	
Procedure ordering physician specialty			
Neurology/Neurosurgery	10,887 (64.9%)		
Medical and Surgical critical care	547 (3.3%)		
Other	5890 (35.1%)		
Payor	10,732 (64.0%)	784,710 (66.5%)	<0.0001
Medicare	2088 (12.4%)	108,204 (9.1%)	
Medicaid	2214 (13.2%)	153,133 (12.9%)	
Other Managed Care	243 (1.4%)	16,317 (1.4%)	
Other government payors	34 (0.2%)	1,403 (0.1%)	
Workers Compensation	1466 (8.7%)	115,650 (9.8%)	
Charlson comorbidity index (Mean, Std)	6.16 ± 2.96	5.97 ± 2.67	<0.0001
Seizure diagnosis	4,787 (28.5%)	74,470 (6.3%)	<0.0001
Cerebrovascular disease present on admission flag	15,393 (91.8%)	1,128,457 (95.7%)	<0.0001
Cerebrovascular disease type			<0.0001
Ischemic stroke *	12,551 (74.8%)	1,009,841 (85.6%)	
Hemorrhagic stroke *	6,864 (40.9%)	240,688 (20.4%)	
Mechanical Ventilation	5,611 (33.4%)	78,678 (6.7%)	<0.0001
Anti-seizure medication use anytime during hospitalization	13,450 (80.2%)	495,692 (42.0%)	<0.0001

	EEG (N= 16,777)	No EEG (N= 1,179,471)	P value
Anti-seizure medication use at admission (Day 0–1)	8,645 (51.5%)	299,866 (25.4%)	<0.0001
Anesthetic use anytime during hospitalization	8,765 (52.2%)	303,583 (25.7%)	<0.0001
Anesthetic medication use at admission (Day 0–1)	4,658 (27.8%)	134,765 (11.4%)	<0.0001
Vasopressor use at admission (Day 0–1)	615 (3.7%)	21,473 (1.8%)	<0.0001
Length of hospital stay (Mean, Std)	12.58 ± 17.29	5.36 ± 9.40	<0.0001
In-hospital mortality	1,863 (11.1%)	67,659 (5.7%)	<0.0001

*Not mutually exclusive (a subset of patients had both ischemic and hemorrhagic stroke ICD codes during an inpatient encounter)

Table 2.

cEEG utilization over time

Year	Total no of Patients receiving EEGs	No. of hospitals performing EEGs	Mean no of EEGs/hospital
2014	713	107	6.67
2015	1,647	178	9.25
2016	2,381	204	11.67
2017	3,099	230	13.47
2018	3,139	228	13.77
2019	3,310	218	15.18
2020*	538	106	5.08*

*Incomplete data