Association of Prevalent Stroke with Hospitalization for Seizure: Patterns and Prognoses

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Introduction: Despite the close relationship between stroke and seizures, little is known about stroke trends and inpatient mortality among patients with seizures. *Materials and Methods*: The National Inpatient Sample was used to analyze the prevalence and trends of stroke among patients discharged with a primary diagnosis of seizures between 2006 and 2014. International Classification of Diseases, Ninth Revision, Clinical Modification was used to identify patients discharged with a primary diagnosis of seizures and those with a secondary diagnosis of stroke. Multivariable logistic regression was used to examine the association between inpatient hospital mortality and stroke. Adjusted prediction of mortality post estimates of logistic regression was used to analyze mortality by stroke status overtime. *Findings*: A total of 400,391 (weighted 1,980,707) patients with seizures were identified between 2006 and 2014, including 61,039 weighted (3%) with a secondary diagnosis of stroke patients. Among patients with a primary diagnosis of seizures, having a secondary diagnosis of stroke doubled the odds of in-hospital death (odds ratio = 2.02; 95% confidence interval: 1.74-2.34; $P < .001$). Overall, between 2006 and 2014, the prevalence of stroke among patients discharged with a primary diagnosis of seizures remained stable at 3% amid fluctuations across years. Among patients with a primary discharge diagnosis of seizures who had stroke, in-hospital mortality increased from 2.3% in 2006 to 3.6% in 2014 but decreased from .8% in 2006 to .7% in 2014 in those without stroke. *Conclusions*: Stroke is prevalent and is associated with increased mortality among patients who are discharged with a primary diagnosis of seizure, with a stable prevalence but suggested increased mortality across time.
Key Words: Seizure—stroke—trends—mortality

Introduction

Seizures and stroke are 2 prevalent neurological conditions in the United States. The number of individuals living with epilepsy (a condition characterized by recurrent seizures or increase risk of seizure recurrence) in the United States is estimated at 3.4 million.[1] Similarly, about 7.2 million adults age 20 years and above reported having had a stroke in 2014, translating into a prevalence of about 2.7%.[2] These figures are expected to increase, fueled by advances in the delivery of acute stroke care, increased stroke survival, and population aging.[3] Current estimates suggest that nearly 11% of all diagnosed epilepsy may be attributable to a history of stroke.[4] As the number of stroke survivors increases, the number of patients with both seizures and stroke is expected to increase concomitantly, particularly among adults and the elderly. In

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addition to epidemiological data, animal models have provided pathophysiologic evidence for the link between stroke and seizures.[5,6] Basic science research has implicated transient biochemical dysfunctions, enhanced excitotoxicity, inflammation, and ischemia in the genesis of seizures during the acute phase of stroke while in the late phase, gliosis with persistent excitotoxicity has been proposed as a mechanism for epileptogenesis.[7] These models have shown that the risk of seizure after stroke increases with hemorrhagic stroke, cortical involvement, large infarct size, and severe strokes.[7,8]

The literature on stroke and seizures has focused heavily on prevalence, risk factors, and mortality of seizures among patients with stroke. To the best of our knowledge, only 1 study enrolling patients aged 60 years and older has provided data on the occurrence of stroke in seizure patients. In that case-control study, stroke occurred 3 times more frequently in those with seizures (Cleary). While contemporary nationwide stroke prevalence and mortality estimates among patients with seizures are lacking, such data has the potential to bring attention to the impact of neurological comorbidities, including stroke, when managing patients hospitalized for seizures. It may also provide critical information needed to reshape priorities in research related to seizures and epilepsy. We aimed at filling this gap by providing an in-depth analysis of the National Inpatient Sample (NIS), the largest database of hospitalized patients in the United State, to explore temporal trends of stroke prevalence and mortality among patients hospitalized for seizure.

Methods

Data

The data source was the Nationwide Inpatient Sample. The NIS is part of the Healthcare Cost and Utilization Project (HCUP) and is sponsored by the Agency for Healthcare Research and Quality (AHRQ) which has developed "the Informed Consent and Authorization Toolkit for Minimal Risk Research to facilitate the process of obtaining informed consent and Health Insurance Portability and Accountability Act (HIPAA)". The NIS contains around 7 million deidentified hospital stays yearly and includes 20% stratified discharge samples from US Community hospitals, excluding rehabilitation and long-term acute care hospitals.[9,10] The NIS is drawn from all States participating in HCUP, covering more than 95% of the US population. The sample is representative of the US population based on the following sampling strata: census division of hospital, hospital ownership, urban-rural location of hospital, hospital teaching status, and number of beds in the hospital.[9] The NIS includes the following files: (1) Inpatient Core File: this inpatient discharge-level file contains a sample of hospital discharge records from participating States; (2) Hospital Weights File: this hospital-level file contains weights and variance estimation data elements, as well as linkage data elements; (3) Disease Severity Measures File: it is a discharge-level file that contains information from the AHRQ Comorbidity Software and information from these files is used in conjunction with the Inpatient Core Files; and (4) Diagnosis and Procedures Group File: this discharge-level file contains data elements derived from AHRQ software tools based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure information in the HCUP databases. We merged the Inpatient Core File with Hospital Weights File, Disease Severity Measures File, and Diagnosis and Procedure Groups File for each year. Finally, we pooled 9 years of data (2006-2014) to perform temporal trend analyses.[9] In order to obtain national estimates, discharge weights are provided along with information necessary to calculate the variance of estimates.[9] Detailed information on the design of the NIS is available on: http://www.hcup-us.ahrq.gov.[11]

Variables of Interest

We included adults aged greater than or equal to 18 years with seizures, identified using the following ICD-9-CMprimary diagnosis codes: 780.3x (for seizure) and 345.xx (for epilepsy ie, recurrent seizure and increased risk of seizures after a single unprovoked seizure). Both 345.xx and 780.39 codes have been endorsed by the ILAE for the definition of seizure in epidemiological studies.[12] Stroke was identified using secondary ICD-9-CM diagnostic codes of ischemic stroke (433.X1, 434.X1, and 436), hemorrhagic stroke (430, 432.0, 432.1, and 432.9), and intracerebral hemorrhage (431) as reported in previous epidemiological studies based on the NIS.[13,14] The primary independent variable in this study was a dichotomous variable '*stroke*' (yes versus no) extracted from the secondary ICD-9-CM diagnostic codes. The dependent variable was a binary variable '*died*' (yes versus no) during hospitalization. We also computed the rate of selected causes of seizures as they may occur in the inpatient setting, coded as secondary discharge diagnoses; these included: brain tumor (ICD-9-CM diagnostic codes: 225.0-225.4, 225.8, 225.9, 199.1, and 191.0-191.9),[15] encephalitis (ICD-9-CM diagnostic codes: 323.9), meningitis (ICD-9-CM diagnostic codes: 320.1-322.9), cerebral abscess (ICD-9-CM diagnostic codes: 324.0 and 324.9),[16,17] alcohol use disorder not in remission (ICD-9-CM diagnostic codes: 303.x),[18] traumatic brain injury (ICD-9-CM diagnostic codes: 800.0, 801.9, 803.0, 804.9, 850.0, 854.1, and 959.01).[19]

Statistical Analyses

We used Stata ver.14 software (College Station, TX: StataCorp LP) to perform the analyses. Complex design surveys require that analyses account for weighting, clustering, and stratification. We applied survey weights in order to generate national population level estimates. We used a multivariable logistic regression model to examine the association between inpatient hospital mortality and stroke controlling for covariates. We input the following covariates: age (18-44 years, 45-64 years, 65-84 year and ≥ 85 years), gender (male, female), race/ethnicity (White, Black, Hispanic, and others), primary payer (medicare, medicaid, private, and self-pay/no charge/others), hospital bed size (small, medium, large), hospital location/teaching status (urban teaching, urban nonteaching, and rural), admission day (weekday, weekend), median household income for patient's ZIP code (quartile 1, quartile 2, quartile 3, and quartile 4), hospital census region (Northeast, Midwest, South, and West), length of stay (LOS) and Charleson comorbidity index (CCI). LOS and CCI were continuous variables given in mean but all other variables were categorical expressed as count and percentages. The number and severity of comorbid conditions were assessed using the modified version of CCI.[20] The CCI is a weight score of 17 conditions but the ICD-9-CM codes related to stroke were not included in the scoring of the index in this study because the condition is accounted for the primary independent variable. We also performed trend analyses to determine any change in the annual prevalence and mortality of stroke among adults with seizure from 2006 to 2014. We used the adjusted predictions of mortality (*marginsplot* command in Stata) post-estimates of logistic regression to examine mortality by stroke status overtime taking into account the complex survey design. We also examined how years differed for stroke and nonstroke using the interaction effect of year and seizure variable. Statistical hypotheses were tested using P less than .05 as the level of significance.

Results

General Characteristics

We included a total of 400,391 (weighted 1,980,707) patients with a primary discharge diagnosis of seizure in the final analysis between 2006 and 2014. Between 2003 and 2014, there was a total of 343,352,727 weighted hospital discharges;[9,10] therefore seizures was the primary diagnosis in .6% of all US hospital discharges during the study period. Three percent of these patients (61,039 weighted) had a secondary discharge diagnosis of stroke. In comparison, 1.8%, 1.2%, .8%, .7%, .5%, and .2% of patients had a secondary discharge diagnosis of brain tumors, encephalitis, meningitis, alcohol use disorder, traumatic brain injury, and cerebral abscess respectively (Fig 1). Stroke patients were more likely to be old, men, non-Hispanic Whites, Medicare beneficiaries, recruited from large hospitals, hospitalized in rural and urban nonteaching hospitals, admitted during weekends, in the low income category, and to live in the Midwest and the South. Compared to those without stroke, patients discharged with a diagnosis of seizure who had a comorbid diagnosis of stroke stayed longer in the hospital and had more medical comorbidities; Table 1.

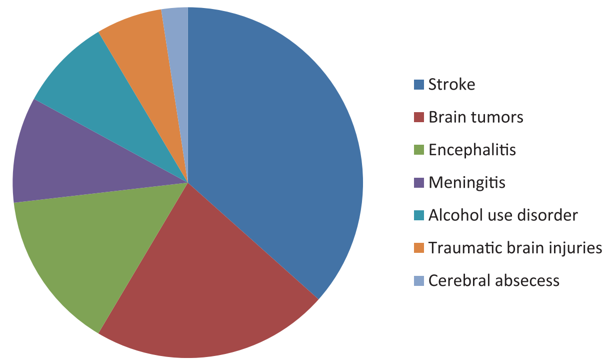

Figure 1. *Secondary discharge diagnoses among patients with seizures.*

Mortality among Patients Discharged with a Primary Diagnosis of Seizures by Stroke Status

Among patients with a primary discharge diagnosis of seizures, having a diagnosis of stroke doubled the odds of in-hospital death compared to those without stroke (odds ratio [OR] = 2.02; 95% confidence interval [CI]: 1.74-2.34; $P < .001$) (Table 2). Patients aged 45-64 years (OR = 1.82; 95% CI: 1.57-2.11), 65-84 years (OR = 3.84; 95% CI: 3.24-4.55), and those aged ≥85 years (OR = 8.25; 95% CI: 6.85-9.94) had a higher odds of in-hospital death than younger patients. Conversely, being hospitalized in an urban nonteaching hospital was associated with an 18% (OR = .82; 95% CI: .70-.95) lower odds of dying. Prolonged LOS (OR = 1.03; 95% CI: 1.02-1.04) and the presence of comorbidities (higher CCI) (OR = 1.29; 95% CI: 1.27-1.31) were associated with higher in-hospital mortality. Compared to year 2006/08, the odds of in-hospital death was lower in the year 2012/14 (OR = .87; 95% CI: .78-.97).

Temporal Trends in Stroke Prevalence and Mortality among Patients Discharged with a Primary Diagnosis of Seizures

Among patients discharged with a primary diagnosis of seizures, the prevalence of stroke increased from 3% in 2006 to 3.7% in 2009, then declined to 2.6% in 2012, and finally increased to 3% in 2014 so that overall it remained unchanged between 2006 and 2014 (Fig 2). Mortality trends pattern among patients discharged with a primary diagnosis of seizures was different by stroke status. Over time, mortality increased from 2.3% in 2006 to 3.6% in 2014 among those with a comorbid diagnosis of stroke but modestly decreased from .8% in 2006 to .7% in 2014 among seizure patients without stroke (Fig 3).

Discussion

The findings of this study covering 9 years of nationwide hospital discharges in the US are the following: (1) stroke was present in 3% of patients who were discharged with a primary diagnosis of seizure, (2) among patients who were discharged with a primary diagnosis of seizure,

Table 1. *Sample demographics and clinical characteristics among adult patents with a comorbid diagnosis of stroke hospitalized for seizure, 2006-2014*

Variables	All (%)	Stroke (%)	No-stroke (%)	*P* value
N (n)	1,980,707 (400,391)	61,039 (12,332)	1,919,668 (388,059)	
Age category				
Age 18-44	36.6	11.5	37.4	<.001
Age 45-64	35.9	33.4	35.9	
Age 65-84	22.1	43.5	21.5	
Age ≥85	5.4	11.6	5.2	
Gender				
Male	48.7	53.7	48.5	<.001
Female	51.3	46.3	51.5	
Race/ethnicity				
Non-Hispanic White	62.6	67.2	62.5	<.001
Non-Hispanic Black	22.0	20.5	22.1	
Hispanic	9.9	7.5	10.0	
Others	5.5	4.8	5.4	
Primary payer				
Medicare	42.7	62.3	42.1	<.001
Medicaid	20.3	12.1	20.6	
Private	24.7	18.1	24.9	
Self-pay/no charge/others	12.3	7.5	12.4	
Hospital bed size				
Small	10.9	10.3	10.9	.024
Medium	24.4	23.4	24.5	
Large	64.7	66.3	64.6	
Urban-teaching status				
Rural	9.6	9.8	9.6	<.001
Urban nonteaching	35.6	38.5	35.5	
Urban teaching	54.8	51.7	54.9	
Admission day				
Week day	76.1	73.8	76.2	<.001
Weekend	23.9	26.2	23.8	
Median household income for patient's ZIP code				
Quartile 1	33.0	31.1	33.1	<.001
Quartile 2	25.3	25.6	25.3	
Quartile 3	22.6	22.5	22.6	
Quartile4	19.1	20.8	19.0	
Hospital census region				
Northeast	23.2	19.3	23.3	<.001
Midwest	22.4	23.1	22.3	
South	37.7	40.7	37.6	
West	16.7	16.9	16.8	
Died				
Yes	.8	2.5	.7	<.001
No	99.2	97.5	99.3	
LOS, mean in days	3.8	5.6	3.7	<.001
Charleson comorbidity index (CCI), mean	.9	1.3	.8	<.001
Year category				
Year 2006/08	32.3	34.3	32.2	<.001
Year 2009/11	34.6	36.1	34.5	
Year 2012/14	33.1	29.6	33.3	

N, weighted sample size; n, unweighted sample size; %, weighted percentage.

having a diagnosis of stroke independently doubles the odds of in-hospital mortality, (3)inpatient mortality has modestly decreased over time among patients discharged with a primary diagnosis of seizure without stroke but an upward trend was observed for those with a comorbid diagnosis of stroke.

Table 2. *Logistic regression model: adjusted odds-ratio for inpatient stroke mortality among adults with seizure.*

Variables	Odds ratio	95% CI	*P* value
Primary independent variable			
No-stroke (ref.)	–	–	–
Stroke	2.02‡	1.74-2.34	<.001
Covariates			
Gender			
Male (ref.)	–	–	–
Female	1.06	.97-1.15	.152
Age category			
Age 18-44 (ref.)	–	–	–
Age 45-64	1.82‡	1.57-2.11	<.001
Age 65-84	3.84‡	3.24-4.55	<.001
Age ≥85	8.25‡	6.85-9.94	<.001
Race/ethnicity			
Non-Hispanic White (ref.)	–	–	–
Non-Hispanic Black	.95	.85-1.05	.356
Hispanic	.94	.80-1.11	.492
Others	1.07	.89-1.29	.443
Primary payer			
Medicare (ref.)	–	–	–
Medicaid	.86	.73-1.02	.088
Private	1.03	.90-1.18	.625
Self-pay/no charge/others	1.12	.92-1.36	.248
Hospital bed size			
Small (ref.)	–	–	–
Medium	.98	.84-1.14	.849
Large	1.04	.90-1.19	.565
Urban-teaching status			
Rural (ref.)	–	–	–
Urban nonteaching	.82†	.70-.95	.011
Urban teaching	.92	.79-1.07	.269
Admission day			
Week day (ref.)	–	–	–
Weekend	1.07	.98-1.18	.116
Median household income for patient's ZIP code			
Quartile 1 (ref.)	–	–	–
Quartile 2	1.07	.96-1.20	.186
Quartile 3	.93	.82-1.05	.294
Quartile4	1.02	.90-1.16	.688
Hospital census region			
Northeast (ref.)	–	–	–
Midwest	.88	.77-1.02	.095
South	1.04	.93-1.16	.418
West	1.05	.92-1.20	.454
LOS, mean in days	1.03‡	1.02-1.04	<.001
Charleson comorbidity index (CCI), mean	1.29‡	1.27-1.31	<.001
Year category			
Year 2006/08 (ref.)	–	–	–
Year 2009/11	.96	.86-1.08	.574
Year 2012/14	.87*	.78-.97	.016

*Level of significance $P < .05$.
†Level of significance $P < .01$.
‡Level of significance $P < .001$.

Neurological and non-neurological comorbidities are frequent among patients with seizures.[21] Several studies have reported on the proportion of stroke patients with seizures;[22,23] however, there are limited data on the frequency of stroke among patients hospitalized for seizure. In the current study, 3% of patients who were discharged with a primary diagnosis of seizure had a diagnosis of stroke. We are not aware of previous

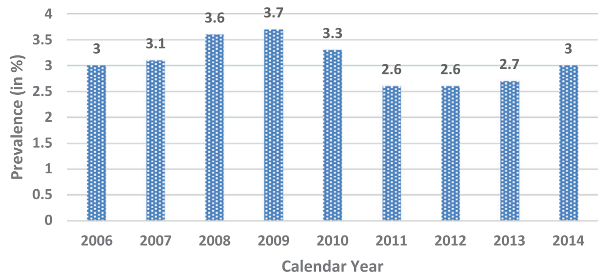

Figure 2. *Trends in prevalence of stroke among adults with seizure, 2006-2014.*

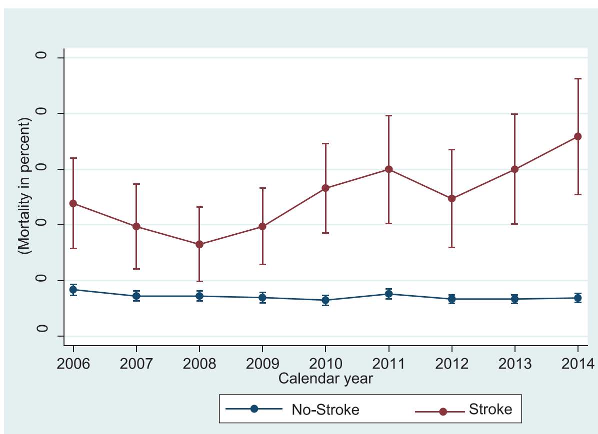

Figure 3. *Adjusted predictions of mortality by stroke status among adults with Seizure (95% CIs).*

nationwide estimates of stroke prevalence among patients with seizure. In a study evaluating the contribution of electroencephalography in the assessment of the risk of seizure among hospitalized patients in 3 major university hospitals in the United States, 1.7% of patients with seizure had a comorbid diagnosis of stroke.[24] A bidirectional relationship between stroke and seizure has been suggested by a high prevalence of seizures among stroke patients in meta-analyses and large population-based epidemiological studies[22,23,25] and the finding that elderly individuals without a history seizure had a 3-fold risk of stroke after their first seizure.[26] Our results further reinforce this concept by providing nationwide stroke prevalence estimates among individuals with a primary discharge diagnosis of seizure.

In this study, having a comorbid diagnosis of stroke independently doubled the odds of in-hospital death. Inpatient mortality among patients with seizure may be related to direct consequences of seizures, particularly convulsive status epilepticus, or to the effects of acute symptomatic causes including anoxic/hypoxic brain injury, traumatic brain injury, and stroke.[27,28] Several studies have reported an increased risk of death in patients with stroke and seizures. The relationship has, however, mainly focused on the possible effect of seizure on mortality among stroke patients.[29] In this study, we built on previous evidence to provide data on the association of stroke and death among patients discharged with a primary diagnosis of seizure.

In addition to providing nationwide prevalence estimates, our study has also shed light on variations of stroke prevalence across time among patients discharged with a primary diagnosis of seizure. Literature pertaining to in-hospital stroke prevalence trend among individuals with seizure is limited. In the current study, we found that there were 2 periods during which national stroke inpatient prevalence increased (2006-2009 and 2011-2014) separated by a periods of prevalence decline (2009-2011) but overall, between 2006 and 2014, the prevalence of stroke in this group of patients was unchanged. Although we cannot explain these fluctuations, our results confirm that stroke is strongly associated with seizure and that the association between both conditions may not have changed over time.

We have also provided updated nationwide overall mortality estimates and trend among patients discharged with a primary diagnosis of seizures by stroke status. Stroke was an independently associated with in-hospital mortality. The presence of stroke in seizure patients may be a marker of seizure severity (ie, status epilepticus). This is suggested by the previous finding that nearly 9 out of 10 deaths within 30 day of hospitalization for status epilepticus were due to acute symptomatic causes, which were dominated by cerebrovascular diseases.[28] Several other predictors of in-hospital mortality were replicated in the current analysis. Prolonged LOS (a surrogate of disease severity), the presence of medical comorbidities, and advanced age (stroke and seizure outcome is worse in elderly compared to young individuals) were independently associated with an increased risk of death. These observations suggest that inpatient mortality among individuals with seizure can be best mitigated by a multilevel and multidisciplinary approach. It is expected that such strategies help clarify the role of stroke and cost-effective interventions to curb inpatient mortality among patients with seizure.

Mortality trends differed by stroke status among patients with seizures. While a downward trend was observed in those without stroke, mortality increased overtime in patients with a diagnosis of stroke. It stands to reason that the sickest patients are more likely to die in the hospital. This assumption is supported in the current study by the positive association between mortality and LOS, medical comorbidities, and advanced age. In this study, there was an independent and positive association between stroke and in-hospital death among patients with seizures, which did not seem to decrease with time. It is possible that in this sample, stroke patients represented a significant proportion of very sick patients with seizures. Studies examining inpatient mortality trend among patients with seizure are scarce and have mainly focused on those with status epilepticus. For example, Betjemann et al have compared mortality for status epilepticus between January 1, 1999 and December 31, 2010, using data from the Centers for Disease Control and Prevention and the NIS. The authors concluded that there was a 5.6% increase in mortality in status epilepticus with the largest increase observed in those who were intubated.[30] Patients who have seizures and a comorbid diagnosis of stroke may represent those at the higher end of severity spectrum; those patients may not have benefited to the same extent as those with less severe symptoms from recent stroke prevention and therapeutic progresses. An alternative explanation for increase in inpatient mortality among seizure patients with comorbid stroke is the relative status quo in the development of specific interventions aimed at directly blocking the cascade of events linking stroke with seizure.

Limitations

This study has limitations that should be accounted for when interpreting its findings. Given its retrospective nature, a misclassification bias is possible, which may not have been systematic across all 9 years. In addition, certain conditions that offer a higher reimbursement than seizure could have been coded as primary discharge diagnosis, potentially overlooking individuals with seizures. Furthermore, we may have not captured all seizures including in particular acute symptomatic seizures and first unprovoked seizures as those patients may not always require hospitalization. Variables such as seizure type, prior history of seizure, electroencephalography/continuous video-electroencephalography results, use antiseizure medications, and brain imaging findings were not included in the analyses as they are generally not collected in the NIS. The current findings do not establish causality which would have required analysis of a prospective cohort of patients with seizure. Finally, safeguards to maintain confidentiality did not allow us to account for multiple discharges from the same individuals contributing to the dataset or that of hospitals individually.

Despite the aforementioned limitations, our study has several strengths including the rigorous and standardized data collection, up-to-date data information with national representativeness irrespective of the hospital size/denomination and insurance status.

Declaration of Competing Interest

The authors do not have any conflicts of interest to declare.

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