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# Mortality and trends in stroke patients with seizures: A contemporary nationwide analysis

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ABSTRACT

*Objective:* Seizures are frequent among stroke patients. The goal of this study was to provide updated trends in seizures prevalence and mortality among hospitalized stroke patients.
*Methods:* Data from the National Inpatient Sample was used to estimate trends in seizures prevalence among stroke patients as well as mortality by seizures status, between 2006 and 2014. We used a logistic regression model to examine the association between seizures and mortality, accounting for extraneous factors.
*Results:* Overall 372,957 patients (6%) stroke patients had a secondary diagnosis of seizures. We found 29% higher odds of in-hospital death among stroke patients with a secondary diagnosis of seizures. The prevalence of seizures was more than two times higher among patients with hemorrhagic stroke (11.4%) compared to those with ischemic strokes (4.8%). The prevalence of seizures among stroke patients was 6.6% and 6.2% for all strokes, 12.6% and 12% for hemorrhagic strokes, and 5.3% and 5% for ischemic strokes respectively in 2006 and 2014. Although there was a steady decline in both groups, mortality rate among hospitalized stroke patients with seizures was consistently higher than in those without seizures for all strokes, ischemic strokes, and hemorrhagic strokes. Compared to patients with ischemic stroke and seizures, mortality rate was higher among patients with hemorrhagic stroke and seizures.
*Significance:* Seizures were present in nearly one out of 15 patients hospitalized for stroke and were more frequent among those with hemorrhagic stroke. There was a decline in mortality among stroke patients during the study period, which remained significantly higher in patients with seizures than in patients without seizures, and in those with hemorrhagic stroke compared to those with ischemic stroke.

## 1. Introduction

Seizures and stroke are among the most prevalent and disabling neurological conditions in the United States. (Benjamin et al., 2017; Zack and Kobau, 2017) There is a close relationship between the two conditions. On one hand, for example, in a population of elderly individuals aged 60 years or older without a history of stroke who experienced their first seizures, Cleary et al have found that the likelihood of developing stroke was almost three times higher than in those without a history of seizures (Cleary et al., 2004). Therefore, the onset of seizures in elderly and probably in older adults may represent an opportunity for stroke prevention. On the other hand, between 2 and 33% of individuals develop seizures within the first two weeks of stroke onset (Camilo and Goldstein, 2004). Seizures at stroke presentation or during hospitalization also have prognostic significance. They are associated with higher mortality and morbidity. Patients who develop seizures at or shortly after stroke also tend to have more severe strokes and prolonged hospitalization (Huang et al., 2014; Burneo et al., 2010). Stroke has now fallen to the fifth cause of death in the United States as a result of intense prevention and therapeutic efforts (Lackland et al., 2014a). Although the decline in stroke mortality has been observed across all age, sex, and racial groups (Lackland et al., 2014a), it remains unclear if these trends transcend stroke complications. More specifically, little is known about mortality trends among patients hospitalized for stroke who have a discharge diagnosis of seizures. An appraisal of the temporal trajectory of prevalence and mortality among stroke patients who have a secondary diagnosis of seizures is needed to optimize treatment strategies and influence outcome in this specific population. This study evaluates the prevalence of seizures and mortality trends among hospitalized stroke patients, using the largest national inpatient

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sample database in the United States, and spanning a 9-year period.

## 2. Methods

### 2.1. Data and subjects

We analyzed data from the National Inpatient Sample (NIS) between 2006 and 2014. The NIS is the largest nationwide all-payer hospital inpatient care database in the United States. It is part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS includes 20% of U.S community hospitals. (Houchens et al., 2016) For the years 2006–2014, the database included all discharges from 1000 hospitals every year, with 7 to 8 million discharges from 42 states (Houchens et al., 2016). We analyzed a sample of 1,256,044 (weighted 6,213,772 U.S population) adults (≥ 18 years) with a primary discharge diagnosis of stroke, including 6% with a secondary diagnosis of seizures. The NIS is publicly available online and does not contain personal identifier, thus, this study qualified for Institutional Review Board waiver.

### 2.2. Diagnosis of stroke and seizure

To identify stroke hospitalizations, we used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) primary diagnostic codes of ischemic stroke (433. × 1, 434. × 1 and 436), hemorrhagic stroke (430, 431, 432.0, 432.1, and 432.9). These codes have been used in previous studies (Burrows et al., 2018; Pickard et al., 2018). Next, we identified stroke individuals with a secondary discharge diagnosis of seizures using secondary ICD-9-CM diagnostic codes of convulsion 780.3x and epilepsy (345.x). The IDC-9-CM codes 780.3x and 345.x have been used in epidemiological studies to identify cases of seizures (McClelland et al., 2010; Mendizabal et al., 2016). Furthermore, using the Montefiore Stroke Registry from January 2009- December 2011 in the United States, There was a 90% concordance between post-stroke seizures diagnosis using these codes and review of medical charts (De Jesus-Alvelo and Labovitz, 2013).

### 2.3. Statistical analysis

We used the STATA ver.14 software (College Station, TX: StataCorp LP) for the current analysis, accounting for the complex sampling design of the NIS. Survey weights were applied in order to generate national population level estimates. Analyses were performed at the person level for all strokes, hemorrhagic strokes, and ischemic strokes. The demographic characteristics of patients were presented by seizures status, as percentages for categorical variables and mean for continuous variables, with differences tested using chi square ($\chi^2$) and t tests, respectively.

The association between seizures and in-hospital mortality among adults with stroke was evaluated using a multivariable logistic regression model. The logistic regression model controlled for the effect of age, sex, race/ethnicity, stroke types, primary payer, hospital bed size, unban-teaching status, admission day, median household income, census region, length of stay (LOS), Charleson Comorbidity Index (CCI) and year of hospitalizations (Ovbiagele, 2010; Lekoubou and Ovbiagele, 2017). Age was coded as 18–44 years, 45–64 years, 65–84 year and ≥ 85 years. Sex was dichotomized as a binary variable. Race/ethnicity was categorized into White, Black, Hispanic, and others. Stroke types were divided into hemorrhagic and ischemic strokes. Primary payer was categorized into Medicare, Medicaid, Private and self-pay/no charge/others. Hospital bed size was grouped into three categories: small, medium and large. Hospital location/teaching hospital status was divided into three groups: urban teaching, urban non-teaching and rural. Admission day was dichotomized as weekday (Monday-Friday) and weekend (Saturday-Sunday). Median household income for patient's ZIP code was classified into four quartiles: quartile 1, quartile 2, quartile 3 and quartile 4. Hospital census region was grouped into Northeast, Midwest, South and West. Death was dichotomized into yes and no. Length of stay (LOS) and Charleson Co-morbidity Index (CCI) were continuous variables expressed as mean and standard deviation. The number and severity of comorbid conditions were assessed using the modified version of the CCI (Quan et al., 2005). The CCI is a weight score of myocardial infarction (weight 1), congestive heart failure (weight 1), chronic pulmonary disease (weight 1), cerebrovascular disease (weight 1), dementia (weight 1), diabetes without complications (weight 1), mild liver disease (weight 1), peptic ulcer disease (weight 1), peripheral vascular disease (weight 1), rheumatologic disease (weight 1), diabetes with complication (weight 2), renal disease (weight 2), malignancy (weight 2), hemiplegia or paraplegia (weight 2), moderate or severe liver disease (weight 3), metastatic solid tumor (weight 6) and HIV/AIDS (weight 6). For this analysis, cerebrovascular disease was excluded as our study population was stroke. We also performed trend analyses to determine any change in the annual prevalence and mortality of seizures among adults with all strokes, hemorrhagic strokes, and ischemic strokes from 2006–2014. For mortality trend analyses, we allowed the effect of year to differ for seizures and non-seizures by computing interaction between "year" and "seizures" variables, therefore generating 95% confidence intervals (CI) to allow comparison across years. Given that ICD-9-CM diagnostic code 345.x is more specific for epilepsy, we performed a "sensitivity analysis" to evaluate the independent association of epilepsy with mortality, excluding those with ICD-9CM diagnostic 780.3x of "convulsion". Statistical hypotheses were tested using $p < 0.05$ as the level of statistical significance.

## 3. Results

### 3.1. Demographics and clinical characteristics of adults with stroke

Between 2006 and 2014, a total of 1,256,044 (weighted 6,213,772) patients were discharged with a primary diagnosis of stroke, including 226,856 (18%) with hemorrhagic stroke and 1,032,940 (82%) with ischemic stroke. In all, 372,957 patients (6%) had a secondary discharge diagnosis of seizures. The prevalence of seizures (rate of patients with a secondary discharge diagnosis of seizures) among patients hemorrhagic stroke was 11.4%, meanwhile seizures prevalence was 4.8% among those with ischemic stroke. The prevalence of seizures varied across pre-specified groups overall and within stroke subtypes (Table 1). Irrespective of the stroke type, seizures prevalence was higher in the age group 18–64 years, Black, Hispanic, Medicaid beneficiaries and self-pay, large hospital bed, urban teaching, weekend admission, quartile 1 income, Northeast, South and West regions. Mean length of stay (LOS) and Charleson Co-morbidity Index (CCI) were higher for individuals with seizures independently of the type of stroke. Unlike ischemic strokes, there was no geographic difference in the distribution of hemorrhagic strokes. Similarly, the prevalence of hemorrhagic strokes was not different across hospital bed size.

### 3.2. Adjusted odds-ratio for seizures mortality among adults with stroke

After adjustment for extraneous factors, having a secondary discharge diagnosis of seizures was associated with a 29% greater odds of hospital death (OR = 1.29; 95% CI: 1.25–1.32) (Table 2). Having a primary diagnosis of hemorrhagic stroke (vs. ischemic stroke) was associated with nearly eight-fold increased odds of in-hospital death. Mortality was higher as aged increased, i.e. 45–64 years vs. 18–44 (OR = 1.20, 95% CI 1.15–1.25), 65–84 years vs. 18–44 years (OR = 1.98, 95% CI: 1.87–2.10), and ≥85 years vs. 18–44 years (OR = 3.60; 95% CI: 3.40–3.83). Non-Hispanic Whites with stroke were 8–10% more likely to die in the hospital respectively compared to Blacks and Hispanics with stroke. Medicare patients had lower odds of

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

| Variables | All Strokes | | | | Hemorrhagic strokes | | | | Ischemic strokes | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All (%) | Seizures (%) | No-Seizures (%) | p-value | All (%) | Seizures (%) | No-Seizures (%) | p-value | All (%) | Seizures (%) | No-Seizures (%) | p-value |
| **N(n)** | 6,213,772 (1,256,044) | 372,957 (75,352) | 5,840,815 (1,180,692) | | 1,110,276 (224,179) | 127,535 (25,751) | 982,740 (198,428) | | 5,103,497 (1,031,399) | 245,338 (49,582) | 4,858,158 (981,817) | |
| ***Age category*** | | | | | | | | | | | | |
| Age 18-44 | 4.4 | 8.1 | 4.2 | < 0.001 | 8.74 | 12.66 | 8.23 | < 0.001 | 3.46 | 5.81 | 3.34 | < 0.001 |
| Age 45-64 | 27.7 | 33.3 | 27.4 | | 32.67 | 36.05 | 32.23 | | 26.64 | 31.91 | 26.38 | |
| Age 65-84 | 50.9 | 45.0 | 51.3 | | 43.66 | 40.66 | 44.05 | | 52.51 | 47.25 | 52.78 | |
| Age $85^{+}$ | 17.0 | 13.4 | 17.1 | | 14.93 | 10.64 | 15.49 | | 17.38 | 15.03 | 17.50 | |
| ***Gender*** | | | | | | | | | | | | |
| Male | 49.6 | 49.4 | 49.6 | 0.289 | 50.21 | 53.98 | 49.72 | < 0.001 | 49.48 | 47.05 | 49.61 | < 0.001 |
| Female | 50.4 | 50.6 | 50.4 | | 49.79 | 46.02 | 50.28 | | 50.52 | 52.95 | 50.39 | |
| ***Race/ethnicity*** | | | | | | | | | | | | |
| White | 72.4 | 64.6 | 72.8 | < 0.001 | 65.30 | 10.98 | 65.69 | < 0.001 | 73.87 | 65.83 | 74.28 | < 0.001 |
| Black | 14.4 | 21.2 | 13.9 | | 15.86 | 14.45 | 15.34 | | 14.06 | 21.90 | 13.66 | |
| Hispanic | 7.3 | 8.4 | 7.3 | | 10.07 | 11.57 | 10.06 | | 6.75 | 7.47 | 6.71 | |
| Others | 5.9 | 5.8 | 6.0 | | 8.77 | 10.1 | 8.91 | | 5.33 | 4.80 | 5.35 | |
| ***Primary payer*** | | | | | | | | | | | | |
| Medicare | 65.7 | 63.3 | 65.9 | < 0.001 | 56.64 | 54.92 | 56.86 | < 0.001 | 67.70 | 67.60 | 67.71 | < 0.001 |
| Medicaid | 6.6 | 10.9 | 6.4 | | 9.22 | 11.98 | 8.87 | | 6.09 | 10.35 | 5.88 | |
| Private | 20.5 | 18.4 | 20.5 | | 24.11 | 23.26 | 24.22 | | 19.64 | 15.93 | 19.82 | |
| Self-pay/no charge/others | 7.2 | 7.4 | 7.2 | | 10.03 | 9.84 | 10.05 | | 6.57 | 6.12 | 6.59 | |
| ***Hospital bed size*** | | | | | | | | | | | | |
| Small | 11.1 | 9.8 | 11.2 | < 0.001 | 6.98 | 6.59 | 7.03 | 0.0626 | 12.03 | 11.46 | 12.06 | 0.0053 |
| Medium | 23.9 | 23.6 | 23.9 | | 20.49 | 20.32 | 20.51 | | 24.65 | 25.31 | 24.62 | |
| Large | 65.0 | 66.6 | 64.9 | | 72.53 | 73.08 | 72.46 | | 63.32 | 63.23 | 63.33 | |
| ***Urban-teaching status*** | | | | | | | | | | | | |
| Rural | 10.5 | 9.2 | 10.6 | < 0.001 | 5.19 | 4.07 | 5.34 | < 0.001 | 11.69 | 11.90 | 11.68 | 0.0020 |
| Urban nonteaching | 38.6 | 35.7 | 38.7 | | 28.56 | 28.33 | 28.59 | | 40.72 | 39.54 | 40.78 | |
| Urban teaching | 50.9 | 55.1 | 50.7 | | 66.25 | 67.60 | 66.07 | | 47.59 | 48.56 | 47.55 | |
| ***Admission day*** | | | | | | | | | | | | |
| Weekday | 78.1 | 75.0 | 78.3 | < 0.001 | 73.97 | 73.82 | 73.99 | 0.5485 | 79.00 | 75.56 | 79.18 | < 0.001 |
| Weekend | 21.9 | 25.0 | 21.7 | | 26.03 | 26.18 | 26.01 | | 21.00 | 24.44 | 20.82 | |
| ***Median household income for patient's ZIP code*** | | | | | | | | | | | | |
| Quartile 1 | 29.2 | 32.2 | 29.0 | < 0.001 | 28.43 | 29.51 | 28.29 | 0.0010 | 29.38 | 33.66 | 29.16 | < 0.001 |
| Quartile 2 | 26.8 | 26.0 | 26.9 | | 25.56 | 25.15 | 25.61 | | 27.07 | 26.41 | 27.11 | |
| Quartile 3 | 23.7 | 22.4 | 23.8 | | 23.76 | 23.07 | 23.85 | | 23.67 | 22.10 | 23.75 | |
| Quartile4 | 20.3 | 19.4 | 20.3 | | 22.25 | 22.27 | 22.25 | | 19.88 | 17.83 | 19.99 | |
| ***Hospital census region*** | | | | | | | | | | | | |
| Northeast | 17.7 | 18.0 | 17.7 | < 0.001 | 17.68 | 18.27 | 17.61 | 0.1818 | 17.68 | 17.81 | 17.67 | < 0.001 |
| Midwest | 22.8 | 21.7 | 22.9 | | 21.14 | 20.65 | 21.21 | | 23.17 | 22.19 | 23.22 | |
| South | 41.0 | 41.6 | 40.9 | | 38.87 | 38.72 | 38.89 | | 41.45 | 43.17 | 41.36 | |
| West | 18.5 | 18.7 | 18.5 | | 22.31 | 22.35 | 22.30 | | 17.71 | 16.83 | 17.75 | |
| LOS, mean in days | 5.2 | 7.7 | 5.0 | < 0.001 | 9.9 | 9.9 | 8.1 | < 0.001 | 4.5 | 6.5 | 4.4 | < 0.001 |
| Charleson Co-morbidity Index (CCI), mean | 1.2 | 1.3 | 1.2 | < 0.001 | 1.1 | 1.3 | 1.1 | | 1.3 | 1.4 | 1.3 | < 0.001 |
| ***Year category*** | | | | | | | | | | | | |
| Year 2003/06 | 33.0 | 34.0 | 32.9 | < 0.001 | 32.82 | 34.14 | 32.64 | < 0.001 | 33.00 | 33.97 | 32.96 | |
| Year 2007/10 | 33.8 | 32.5 | 33.9 | | 34.57 | 32.66 | 34.81 | | 33.68 | 32.42 | 33.74 | |
| Year 2011/14 | 33.2 | 33.5 | 33.2 | | 32.62 | 33.20 | 32.54 | | 33.32 | 33.60 | 33.30 | |

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

hospital death when compared to other "primary payer" groups. Hospital bed size was also independently associated with in-hospital mortality; in general, mortality was higher in larger beds hospitals. Stroke patients were less likely to die if they were in urban non-teaching hospitals (OR = 0.80, 95%CI: 0.76–0.98) or in urban teaching hospitals (OR = 0.90, 95% CI: 0.86–0.95). Similarly higher income was associated with lower mortality. Weekend admissions were associated with 21% higher odds of in-hospital death. Higher mortality rate was also noted in the Northeast compared to other regions. Differences in in-patient mortality was also apparent across years with lower mortality noted in more recent years (2007/10: OR = 0.90; 95% CI: 0.87–0.93 and 2011/14: OR = 0.83; 95% CI: 0.80 – 0.86 vs. 2003/2006). An inverse association was noted between in-patient mortality and length of stay (OR = 0.97; 95% CI: 0.96–0.97) while higher medical comorbidities was associated with a higher odds of in- hospital death (OR = 1.12; 95% CI: 1.11–1.13).

**"Sensitivity analysis" of the independent association between epilepsy and mortality.** An independent and positive association was

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

| Variables | Odds ratio | 95% CI | p value |
|---|---|---|---|
| **Primary independent variable** | | | |
| No-Seizures (Ref.) | – | – | – |
| Seizures | 1.29*** | 1.25–1.32 | < 0.001 |
| **Stroke type** | | | |
| Ischemic strokes (Ref.) | – | – | – |
| Hemorrhagic strokes | 7.83*** | 7.6–8.0 | < 0.001 |
| **Covariates** | | | |
| *Gender* | | | |
| Male (Ref.) | – | – | – |
| Female | 1.16*** | 1.14–1.18 | < 0.001 |
| *Age category* | | | |
| Age 18-44 (Ref.) | – | – | – |
| Age 45-64 | 1.20*** | 1.15–1.25 | < 0.001 |
| Age 65-84 | 1.98*** | 1.87–2.1 | < 0.001 |
| Age $85^{+}$ | 3.60*** | 3.40–3.83 | < 0.001 |
| *Race/ethnicity* | | | |
| Non-Hispanic White (Ref.) | – | – | – |
| Non-Hispanic Black | 0.92*** | 0.89–0.95 | < 0.001 |
| Hispanic | 0.90*** | 0.86–.94 | < 0.001 |
| Others | 1.03 | 0.99–1.07 | 0.062 |
| *Primary payer* | | | |
| Medicare (Ref.) | – | – | – |
| Medicaid | 1.49*** | 1.41–1.57 | < 0.001 |
| Private | 1.21*** | 1.15–1.27 | < 0.001 |
| Self-pay/no charge/others | 2.03*** | 1.89–2.17 | < 0.001 |
| *Hospital bed size* | | | |
| Small (Ref.) | – | – | – |
| Medium | 1.03 | 0.98–1.09 | 0.184 |
| Large | 1.09*** | 1.4–1.14 | < 0.001 |
| *Urban-teaching status* | | | |
| Rural (Ref.) | – | – | – |
| Urban nonteaching | 0.80*** | 0.76–0.84 | < 0.001 |
| Urban teaching | 0.90*** | 0.86–0.95 | < 0.001 |
| *Admission day* | | | |
| Week day (Ref.) | – | – | – |
| Weekend | 1.21*** | 1.19–1.23 | < 0.001 |
| *Median household income for patient's ZIP code* | | | |
| Quartile 1 (Ref.) | – | – | – |
| Quartile 2 | 0.95*** | 0.92–0.97 | < 0.001 |
| Quartile 3 | 0.92*** | 0.89–0.94 | < 0.001 |
| Quartile4 | 0.94*** | 0.90–.97 | < 0.001 |
| *Hospital census region* | | | |
| Northeast (Ref.) | – | – | – |
| Midwest | 0.80*** | 0.76–0.84 | < 0.001 |
| South | 0.89*** | 0.85–0.92 | < 0.001 |
| West | 0.90*** | 0.86–0.94 | < 0.001 |
| LOS, mean in days | 0.97*** | 0.96–0.97 | < 0.001 |
| Charleson Co-morbidity index (CCI), mean | 1.12*** | 1.11–1.13 | < 0.001 |
| *Year Category* | | | |
| Year 2003/06 (ref) | – | – | – |
| Year 2007/10 | 0.90*** | 0. 87–0.93 | < 0.001 |
| Year 2011/14 | 0.83*** | 0.80–0.86 | < 0.001 |

*Level of significance $p < 0.05$; ** level of significance $p < 0.01$, ***level of significance $p < 0.001$.

noted between epilepsy and mortality although the magnitude of the association was less than that of seizures with mortality (8% increase vs. 29%). In this model, the association between other covariates and mortality was unchanged (Supplemental Table 1) (Fig. 1).

### 3.3. Trends of seizures prevalence and mortality among adults with stroke

The prevalence of seizures was highest at the beginning of the study period in 2006 for all strokes (6.6%), hemorrhagic strokes (12.6%) and ischemic strokes (5.3%). A nadir was reached for all strokes (5.6%), hemorrhagic strokes (10.4%), and ischemic strokes (4.6%) in 2009. At the end of the study period in 2014, seizures prevalence was 6.2% for all strokes, 12% for hemorrhagic strokes, and 5% for ischemic strokes (Fig. 2). Among all stroke patients with a secondary discharge diagnosis of seizures, mortality rate was 12.9% (95% CI: 12.2%–13.7%) in 2006 and declined to 10.3% (95% CI: 9.6%–10.9%) in 2014. There was also a decrease in mortality rate among patients with hemorrhagic stroke and seizures from 24.6% (95% CI: 23.7%–25.5%) to 20.9% (95% CI: 20.3%–21.6%). A similar trend was observed among patients with ischemic stroke and seizures as mortality rate decreased from 9.4% (95% CI: 8.0%–10.1%) to 6% (95% CI: 5.0%–7.0%). Mortality rate among patients with stroke but no secondary diagnosis of seizures was generally lower than in those with stroke and seizures and also followed a downward trend i.e. from 7.6% (95% CI: 7.2%–7.9%) to 6.4% (95% CI: 6.0%–7.0%) for all strokes, non-significant trend from 19.5% (95% CI: 18.2–20.9%) to 17.5% (95% CI: 16.1%–19.0%) for hemorrhagic strokes, and from 4.1% (95%CI: 3.9%–4.3%) to 3.6% (95% CI: 3.5%–3.7%).

## 4. Discussion

In this retrospective analysis spanning the period from 2006 through 2014 and using the largest US national inpatient sample, we have found that: 1) overall, one out of 15 patients with stroke had a secondary discharge diagnosis of seizures, 2) the prevalence of seizures was more than two times higher among patients with hemorrhagic stroke (11.4%) compared to those with ischemic strokes (4.8%), 3) The prevalence of seizures among stroke patients was 6.6% and 6.2% for all strokes, 12.6% and 12% for hemorrhagic strokes, and 5.3% and 5% for ischemic strokes respectively in 2006 and 2014, 4) despite a steady decline in both groups, mortality rate among hospitalized stroke patients with seizures was consistently higher than in those without seizures for all strokes, ischemic strokes, and hemorrhagic strokes.

Prevalence estimates from the current study are in line with previous observations, reinforcing the knowledge that seizures are frequent among stroke patients. We found that 6% of hospitalized stroke patients had seizures, which is in the range of 5 to 9% reported in the largest meta-analysis on stroke and seizures that totalized more than 100,000 stroke patients from 34 longitudinal studies (Zou et al., 2015). As previously reported (Zhang et al., 2014), in the current analysis, the rate of seizures was higher among patients with hemorrhagic stroke compared to those with ischemic stroke. In the absence of specific stroke severity scales such as the National Inpatient Sample which are not available in the National Inpatient Sample, disease severity was accounted for in this analysis by the use of the Charleson comorbidity index (CCI). Higher CCI was associated with more seizures in this sample of patients with stroke. Independently of the nature of the underlying etiology, seizures especially when prolonged may result in neuronal loss and dysfunction by enhancing excitotoxicity, inflammation, and ischemia (Scott, 2014). It is purported that in the setting of focal brain ischemia or hemorrhage (with resultant penumbral hematoma and ischemia) the deleterious effects of seizures may even be exacerbated with a direct dose-response relationship between the size of stroke and depolarization event (Pinard et al., 2002). Seizures may be marker of disease severity as suggested by the finding in the current study that patients with seizures had more comorbidities and a prolonged length of hospital stay irrespective of the type of stroke.

The current study has also provided additional evidence of the independent increased risk of hospital death associated with seizures among stroke patients. Recent studies have consistently found higher inpatient mortality among stroke patients with seizures. Unlike previous studies on the relationship between seizures and stroke mortality, the current study had a national reach and included more than 6,000,000 weighted stroke populations among which more than 370,000 had seizures. We have also controlled for the effect of stroke type, an important predictor of mortality as confirmed in the current study (van Asch et al., 2010). In the current study, some variables associated with stroke mortality were counterintuitive. Although mortality has consistently been reported to be higher among the Black population with stroke compared to non-Hispanic White population,

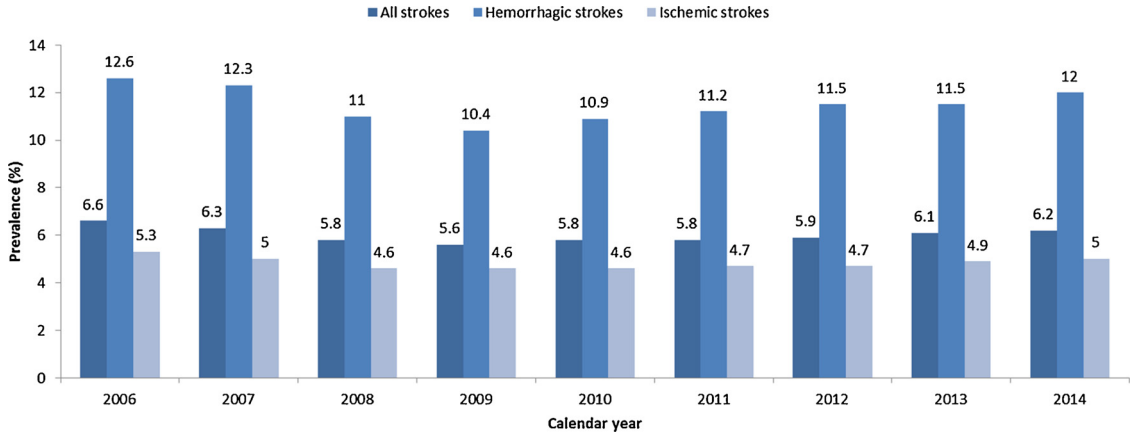


**Fig. 1.** Trends in Seizure prevalence among patients with stroke:2006–2014.

(Limdi et al., 2016) in the current study Black patients with stroke were less likely to die than their non-Hispanic White counterparts, even after controlling for several factors. Similarly contrary to previous reports (McManus et al., 2015), mortality was lower among Medicare beneficiaries. Furthermore, mortality rates among stroke patients have traditionally been lower in the Northeast where there is a greater access to healthcare compared for example to the Southeast (Williams et al., 2003); however in the current study, odds of in-hospital death was 10–20% lower in other region than in the Northeast. We could not completely explain the discrepancy between our findings and those of previous studies. Residual confounders not captured in our model could partly account for these results.

The results of this study stretch beyond seizures point prevalence and mortality estimates among hospitalized stroke patients as the study also sheds light on trends for both estimates over a 9-year period. There was an initial decline in seizures prevalence between 2006 and 2009, followed by an increase between 2010 and 2014 without reaching the level of 2006 but overall a modest decline in seizures prevalence was suggested from 2006 and 2014 for all strokes, ischemic strokes and hemorrhagic strokes. The initial decline in seizures among hospitalized stroke patients could potentially be a reflection of the decline in stroke severity, a proxy of stroke size. Stroke size is an important risk factor for seizures and has been declining over the past years. Evidence from observational studies, meta-analyses, and clinical trials suggest that the decline in ischemic stroke severity is accounted for by an increased utilization of antithrombotic (O'Donnell et al., 2006), recombinant tissue plasminogen activator (Wardlaw et al., 2012), treatment of stroke patients in organized stroke units (Limdi et al., 2016; Stroke Unit Trialists' Collaboration, 2013), and possibly cholesterol lowering drugs (Olsen et al., 2007). Furthermore, with the increasing use of recombinant tissue plasminogen activator, higher rate of recanalization are now observed (Rha and Saver, 2007), which may contribute to smaller infarct size and less cortical involvement and ultimately lower seizures risk in stroke patients. It is possible that in the recent years, preadmission blood pressures have been lower in patients with intracerebral hemorrhage as a result of improved blood pressure control at the population level (Lackland et al., 2014b). Patients with intracerebral hemorrhage may also be treated more aggressively (more intensive blood pressure control) and admitted to comprehensive stroke center, potentially resulting in smaller hemorrhage size and therefore lower seizures rates (Anderson et al., 2010; McKinney et al., 2015). The increase in seizures prevalence in the second half of the study period could reflect a nationwide rise in long term electro-encephalography recordings and hence seizures detection rates including subclinical seizures previously unrecognized in the absence of this diagnostic tool.

Another particularity of the current analysis is the provision of mortality trends among hospitalized stroke patients by seizures status. Although a decline in mortality was observed in both groups, a large and nearly static difference was observed between stroke individuals with seizures and those without seizures. Mortality declined in both ischemic and hemorrhagic strokes and remained higher for patients with hemorrhagic stroke. These findings suggest that the decline in stroke mortality since the early 20$^{th}$ century has continued and transcended to hospitalized stroke patients independently of their seizures status. Several factors could account for the persisting excess mortality in stroke patients with seizures. First, the presence of seizures has been associated with stroke severity, and independent predictor of mortality. This is suggested in the current study by a higher level of comorbidity, a lower seizures rate among routinely discharged patients, and more prolonged length of stay among stroke patients. Second, hypertension which is arguably the strongest factor that has contributed to the decline in stroke mortality does not appear to directly and specifically affect the cascade of events leading to death after the onset of seizures. A proposed model suggests that epileptiform activities especially when prolonged increase brain lactate, oxygen and glucose consumption and ultimately the size of the infarcted brain area. Furthermore, seizures have been associated with increased midline shift after hemorrhagic stroke (Vespa et al., 2003). Unfortunately, there is to date no evidence that administering anti-epileptic drugs in the acute phase of stroke reduces the risk of seizures or mortality (Wang et al., 2017).

## Limitations

Interpretations of the results of this study should account for its potential limitations. First, our estimates were based on ICD-9 codes diagnostic which are primarily collected for the purpose of patient care and hence are subject to misclassification; however, it is unlikely that such errors were systematic across the 9-year study period. Second, Individuals-level and/or hospitals-level data with potential impact on trends such as seizures type, stroke etiologies (i.e. small vessel disease vs. cardio-embolic vs. large artery disease vs. cryptogenic), electrocencephalography results including long term electroencephalography, anti-seizure medications, brain MRI findings, stroke severity (i.e. National Institute of Health Stroke Scale), treatment received including prophylactic anti-epileptic treatment, change in hospital management/infrastructure, and withdrawal of care policies were not available. Third, the current study informs us on the association between seizures and stroke; we could not establish any causality, in particular the presence of a prior diagnosis of seizures could not be ascertained. Finally, we could not capture acute stroke that did not result in a hospitalization. Despite these limitations, the current study has strengths. Our estimates are based on up-to-date and large nationally and rigorously collected standardized database. We use accounted for the effect of confounders on the association between seizures and in hospital

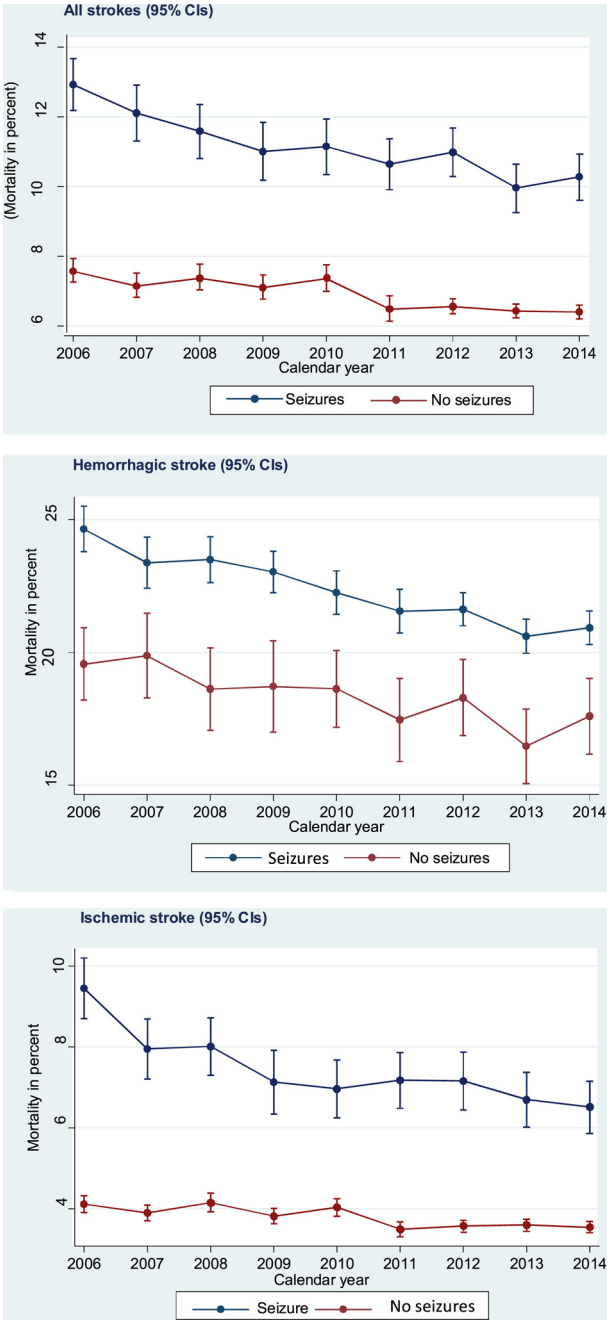


**Fig. 2.** Trends in mortality among stroke patients by seizure status: 2006-2014.

mortality. Furthermore, diagnoses were made by clinicians. We are not aware of any previous attempt to provide contemporary nationally representative of the nation.

## Author contributions

Alain Lekoubou- Study concept and design, data interpretation, and critical revision of the manuscript for important intellectual content. Kinfe Bishu- Study concept and design, statistical analysis and data interpretation, and critical revision of the manuscript for important intellectual content. Bruce Ovbiagele- Study concept and design, critical revision of the manuscript for important intellectual content, and study supervision.

## Declaration of Competing Interest

The authors have no financial conflicts.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.106166.

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