Seizure 41 (2016) 66–69

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Association between seizures and mortality in patients with aneurysmal subarachnoid hemorrhage: A nationwide retrospective cohort analysis

Barret Rush[a,b,*], Katie Wiskar[a], Clark Fruhstorfer[c], Paul Hertz[d]

[a] Division of Critical Care Medicine, Department of Medicine, Vancouver General Hospital, University of British Columbia, Room 2438, Jim Pattison Pavilion, 2nd Floor, 855 West 12th Avenue, Vancouver, British Columbia V5Z 1M9, Canada
[b] Harvard T.H. Chan School of Public Health, Harvard University, 677 Huntington Avenue, Boston, MA 02115, USA
[c] Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[d] Division of General Internal Medicine, Department of Medicine, University Health Network, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 10 April 2016
Received in revised form 7 July 2016
Accepted 16 July 2016
Available online xxx

Keywords:
Subarachnoid hemorrhage
Seizures
Outcomes
United States

ABSTRACT

Purpose: The impact of seizures on outcomes in patients with subarachnoid hemorrhage (SAH) is not well understood, with conflicting results published in the literature.
Method: For this retrospective cohort analysis, data from the Nationwide Inpatient Samples (NIS) for 2006–2011 were utilized. All patients aged ≥18 years with a primary admitting diagnosis of subarachnoid hemorrhage were included. Patients with a diagnosis of seizure were segregated from the initial cohort. Multivariable logistic regression modeled the risk of death while adjusting for severity of SAH as well as co-morbidities. The primary outcome of this analysis was in-hospital mortality.
Results: 12,647 patients met inclusion criteria for the study, of which 1336 had a diagnosis of seizures. The unadjusted in-hospital mortality was higher for patients with seizures compared to those without (16.2% vs 11.6%, $p < 0.01$). Compared to patients without seizures, patients with seizures were younger (52.4 years SD 13.9 vs 54.8 years, SD 13.6; $p < 0.01$), more likely to be male (35.6% vs 31.0%, $p < 0.01$) and had longer hospital stays (18.3 days, IQR 12.0–27.5 vs 14.8 days, IQR 10.0–21.9; $p < 0.01$). After adjusting for the severity of SAH, seizures were found to be associated with increased mortality (OR 1.57, 95% CI 1.32–1.87, $p < 0.01$).
Conclusion: In this large nationwide analysis, the presence of seizures in patients with SAH was associated with higher in-hospital mortality. This finding has potentially important implications for goals of care decision-making and prognostication, but further study in the area is needed.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a significant cause of morbidity and mortality, affecting 2–16 people per 100,000 population [1]. Despite decreased mortality rates in recent decades, many survivors have residual deficits and poor neurologic outcomes [2].

Seizures are a recognized complication of aSAH, occurring in up to 26% of patients [3–6]. While it appears that seizures are correlated with worse grading of aSAH, their effect on patient outcomes remains unclear [7]. Several studies have suggested an association between seizures and poor outcomes, but others show no clear effect [3,7–13,19,20]. Most studies to date have been single-center trials, with the potential for variations in care delivery and patient demographics.

The National Inpatient Sample (NIS) is a large inpatient database in the United States that captures over eight million hospital stays annually [14]. The aim of our study was to use a large, nationally-representative dataset to investigate the association between seizures and hospital mortality in a real-world cohort of patients with aSAH in the United States from 2006 to 2011.

2. Methods

Our study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)

* Corresponding author at: Division of Critical Care Medicine, Department of Medicine, Vancouver General Hospital, University of British Columbia, Room 2438, Jim Pattison Pavilion, 2nd Floor, 855 West 12th Avenue, Vancouver, British Columbia V5Z 1M9, Canada.
E-mail addresses: bar890@mail.harvard.edu (B. Rush), katiewiskar@gmail.com (K. Wiskar), clark.fruhstorfer@gmail.com (C. Fruhstorfer), paul.hertz@uhn.ca (P. Hertz).

http://dx.doi.org/10.1016/j.seizure.2016.07.008
1059-1311/

statement [15]. A de-identified dataset was used for this analysis, for which a waiver of consent was obtained from the University of British Columbia Institutional Review Board (H15-01943). The primary outcome for this study was in-hospital mortality.

2.1. Study population

We performed a retrospective cohort review using the Nationwide Inpatient Sample (NIS) for 2006–2011. The NIS is a federal all-payer database produced by the Agency for Healthcare Research and Quality (AHRQ) that captures approximately 20% of all inpatient hospital admissions across the United States. The NIS is a complex survey powered to produce national projections representing approximately 95% of all inpatient care delivered in the United States [14].

Patients ≥18 years of age with a primary admitting diagnosis of aSAH based on *International Classification of Disease 9th edition* (ICD9) code 430 were isolated from the database. Only patients who had ICD9 codes for either endovascular (39.72, 39.75, 39.76, 39.79) or open treatment (39.51) of aneurysms were included in the cohort. This was done to ensure that the cohort represented patients who were actively managed in treatment of their aneurysm [16]. Seizures were defined using ICD9 codes for epilepsy and convulsions, which have been independently validated for the study of seizures [17]. The presence of seizures was defined as a patient having codes for epilepsy (345.0*x*–345.5*x* and 345.7*x*–345.9*x*) or other convulsions (780.39), similar to other published literature [12].

Patient level characteristics obtained from the database included age, gender, in-hospital mortality, the 29 Elixhauser comorbidity indices, and length of stay (LOS) [18]. Hospital characteristics gathered included size (small, medium, large as defined by the AHRQ [14]), region of the country (West, Northeast, Midwest and South), and teaching status (yes vs no).

In order to account for the severity of aSAH, we employed the Nationwide Inpatient Sample Subarachnoid Severity Scale (NIS-SSS) developed by Washington et al. [19]. The NIS-SSS was independently validated to be equivalent to the Hunt and Hess score for predicting six month functional outcomes based on the Modified Rankin Score. Variables included in the NIS-SSS are coma (ICD9 780.01, 780.03), aphasia (438.1–438.89), stupor (780.02, 780.09), paresis/plegia (438.2–438.53, 781.4), cranial nerve deficits (378.5–378.56, 379.4–379.43), CSF shunting (02.31–02.39), and mechanical ventilation (96.04, 96.7–96.72).

2.2. Statistical analysis

Data were analyzed using SAS v9.4 (Cary, NC). Complex weights were used throughout all calculations, enabling appropriate national projections. Percentages in all tables and figures reflect national estimates. Chi-squared and independent *t*-tests were used for univariate analysis where appropriate. All statistical modeling was performed with an alpha significance of 0.05 (Fig. 1).

A logistic regression model was created utilizing the PROC SURVEYLOGISTIC function in SAS. Variables included in the model of mortality were age, gender, presence of seizures, NIS-SSS score, hospital size, hospital teaching status, hospital region, and the 29 Elixhauser co-morbidity indices. In order to produce accurate results, we removed the ICD9 codes for seizures from the Elixhauser "other neurological disorder" index for the purposes of this analysis.

3. Results

We examined a total of 47,911,414 hospitalizations from the 2006 to 2011 NIS samples. We identified 12,647 patients with aSAH who met the inclusion criteria for the study, of whom 1336 (10.6%) also carried a diagnosis of seizures. The unadjusted in-hospital mortality was higher for patients with seizures compared to those without (16.2% vs 11.6%, p 0.01; Table 1). Compared to those without seizures, patients with seizures were younger (52.4 years SD 13.9 vs 54.8 years, SD 13.6; $p < 0.01$), more likely to be male (35.6% vs 31.0%, $p < 0.01$) and had longer hospital stays (18.3 days, IQR 12.0–27.5 vs 14.8 days, IQR 10.0–21.9; $p < 0.01$). The NIS-SSS was higher for patients with seizures compared to those without seizures in univariate analysis (8.5 IQR 1.5–21.8 vs 2.4 IQR 1.0–15.0; $p < 0.01$). There was no association between seizures and hospital size ($p = 0.76$), region ($p = 0.08$) or teaching status (0.28).

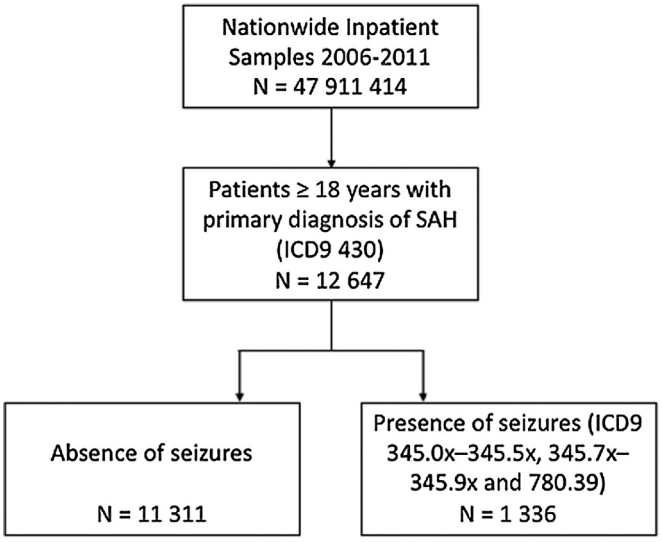

Fig. 1. Patient cohort selection diagram.
This is the wrong figure, this Figure 1 is from the original submission, not the revision. The final cohort was much smaller.

Seizures were found to be associated with increased mortality after adjusting for other variables (OR for death 1.57, 95% CI 1.32–1.87, $p < 0.01$) (Table 2). Variables associated with increased mortality in aSAH included: age (per 5 year increase OR 1.16, 95% CI 1.13–1.19, $p < 0.01$), NIS-SSS (OR 1.019, 95% CI 1.017–1.020, $p < 0.01$), chronic lung disease (OR 1.23, 95% CI 1.04–1.44, $p = 0.01$), liver disease (OR 1.91, 95% CI 1.25–2.93, $p < 0.01$), and renal failure (OR 1.72, 95% CI 1.24–2.39, $p < 0.01$).

4. Discussion

In this large, nationally-representative retrospective review, we found that seizures were associated with increased hospital mortality in patients with aSAH. Seizures were more common in younger male patients, and in patients with higher NIS-SSS scores.

Prior research offered conflicting views on the impact of seizures on outcomes in aSAH. While most existing literature supports the association of seizures with worse outcomes [8–11,19,20], several recent groups have reported either a lack of association, or even an association with positive outcomes [3,7,12,13]. Methodological issues may explain this discrepancy. One study excluded patients "comatose or considered unlikely to survive for more than one week", potentially selecting a non-representative cohort of those with less severe presentation [13]. Others focused exclusively on early-onset seizures, despite evidence that seizures may occur later in the disease course [3,7,21]. Furthermore, the detection of seizures, particularly subclinical seizures, may be a proxy for higher-intensity neuro-critical care, which may mitigate their deleterious effect [3].