Research Article

Trends in the Management of Intracranial Vascular Malformations in the USA from 2000 to 2007

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Objective. To assess prevalence, clinical characteristics, trends in treatment pattern, and outcome in patients with intracranial vascular malformations (IVMs).

Methods. Nationwide inpatient sample. Patients with the diagnosis of an IVM admitted to US hospitals from 2000 to 2007. Results. In 58,051 IVM-related admissions (detection rate 2.4/100,000 person-years; mean age 49 ± 17 years; 52% women) major diagnoses were intracranial hemorrhage (ICrH) in 15%, seizure 32%, ischemia 5%, and headache 9%. Procedures included surgery (13%), embolization (13%), radiation therapy (2%), aneurysm clipping (1%), and mechanical ventilation (6%). Ventilation and ICrH were associated with death (2%), whereas ventilation, ICrH, surgery, seizure, and ischemia were associated with unfavorable outcome (20%). IVM detection rate and hospital outcome remained stable over time, whereas mean age and comorbid diagnosis of cerebral ischemia increased (ICrH and seizure decreased).

Conclusion. IVMs are infrequent and present in 1/6 patients with some form of ICrH. Overall, seizure is the dominant comorbid diagnosis (1/3 patients). IVMs are equally prevalent among race-ethnic groups and are increasingly detected later in life. The inpatient care of IVM patients results in death or discharge into specialized care in 1/5 patients.

1. Introduction

Although relatively infrequent, congenital intracranial vascular malformations (IVMs) represent an important cause of intracranial hemorrhage with potentially devastating consequences for the patient [1, 2]. Brain arteriovenous malformations (BAVMs) and cavernous malformations (CMs) are the most important forms among IVMs. The detection rate of BAVMs ranges between 1.1–1.4/100,000 person-years and is approximately 2.2/100,000 person-years for all other forms of IVMs, including CM, venous malformation (VM), vein of Galen malformation, and dural AV fistula, respectively [2–4].

Current management of IVMs is an interdisciplinary challenge, involving neurosurgery, interventional neuroradiology, radiation therapy, and neurology. The potentially deleterious effects of IVM-related intracranial hemorrhage (ICrH) and the risk of recurrent bleeds led to the current paradigm of obliterating the lesion, if deemed feasible with surgery, which appears logical and cause driven [5–7]. In contrast, some large case series found that most patients fared relatively well after the initial hemorrhage from ruptured BAVMs when compared to other causes of ICrH [8–11]. An ongoing multi center clinical trial, ARUBA, will compare the clinical outcome in patients with unruptured BAVMs randomized either into surgical interventional treatment or medical observation (natural history) [12, 13].

Currently, the management patterns vary across centers and may include patients with and without symptoms, with or without intracranial hemorrhage, and with incidentally found IVMs [5]. Specifically, BAVMs often undergo presurgical embolization in an attempt to devascularize the lesion for safer definitive surgery [6, 14]. Radiation therapy is another adjunct treatment form and also a sole option for
lesions that are otherwise not accessible [14, 15]. Adding to the complexity of the procedures and the overall risk, multiple treatment sessions may be necessary and a small rate of recurrence after angiographically confirmed complete removal has been reported [16]. The goals of the present study are to determine the detection rate of IVMs, to assess patient and clinical characteristics, and to analyze treatment pattern and outcome in patients with IVMs admitted to US hospitals. In addition, a trend analysis is performed on above parameters and on hospital cost using nationwide data from year 2000 to 2007.

2. Methods

The Nationwide Inpatient Sample (NIS) is part of the Healthcare Cost and Utilization Project (HCUP) which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) of the US Department of Health & Human Services and represents the largest all-payer inpatient care database in the USA [17]. Datasets from year 2000 to 2007 were analyzed that included 7.4–8.0 million hospital admissions per year from 28 to 40 states and 994–1,044 nonfederal hospitals, respectively. This constitutes a 20% representative and stratified sample of US hospitals. The NIS contains only deidentified data.

Variables included demographic parameters, admission type, length of stay, discharge disposition, death, hospital location, and charges. In addition, relevant diagnoses and procedures in the database were identified using the ICD-9-CM system (The International Classification of Diseases, 9th Revision, Clinical Modification): adult patients (≥18 years) with IVM were selected using code 747.81 (Figure 1). Intracranial hemorrhages were identified using codes 430, 431, and 432.x, seizure using code 345.xx, and headache with 346.xx and 784.0, unruptured cerebral aneurysms with 437.3, and acute ischemic stroke with 433.xx and 434.xx, respectively. Procedures were selected using codes 88.41 (cerebral angiogram), 39.72 and 39.79 (embolization), 01.59 (surgery), 92.3x (radiosurgery), 39.5x (aneurysm clipping), and 96.7x (mechanical ventilation). The NIS collects up to 15 diagnoses and procedures for each admission. Thus, relevant modes of presentation, including intracranial hemorrhage, seizure, and headache were identified by selecting primary diagnoses only in addition to diagnoses found at “ANY” rank.

Analyses were weighted with provided discharge weight data that are used to create national estimates. For the trend analysis data were stratified into four two-year blocks. Univariate analyses included frequency (absolute number and %) and average values (SD; standard deviation) with respective comparative analyses ($\chi^2$-test, $t$-test for independent samples). In multivariate logistic regression models, the risk (odds ratio and 95% confidence interval; OR 95%-CI) of death and unfavorable discharge outcome (death or discharge, other than routine or to short-term hospital) was determined with input of significant and relevant variables from the univariate analysis. In addition, outcome was assessed for patients presenting with hemorrhage versus without. Outcome was further stratified into one group undergoing surgery and the other without surgery. Furthermore, factors were determined that were associated with hospital charges in multivariate linear regression models. A statistical test was considered significant when $P < 0.05$. All statistics were calculated with SPSS 15.0 (Chicago, IL).
3. Results

3.1. Detection Rate. In the years from 2000 to 2007 a total of 58,051 admissions included the diagnosis of an IVM (Table 1). This is approximately 0.02% of all admission (total number of admissions \( n = 306,447,670 \)) and results in an annual hospital detection rate of approximately 2.4 IVM patients per 100,000 person-years in the US (average USA population 300 Million).

3.2. Patient Characteristics and Clinical Variables. Most admissions were acute admissions (63%) (Table 1). In average the primary diagnosis was ICrH in 11%, headache, seizure, or cerebral ischemia in 13%, IVM in 46%, and 31% had other primary diagnoses. However, 28,760 (35%) patients had none of the typical “symptoms,” including ICrH, seizure, headache, or cerebral ischemia.

3.3. Procedures and Outcome. The most frequent procedure was cerebral angiogram with 37%, followed by embolization and surgery with 13% in each category (Table 1). In 72% none of above procedures was performed. Mechanical ventilation was necessary in 6% of the admissions. The average length of stay was 6 ± 8 days. In-hospital death occurred in 2% of the patients and unfavorable outcome, including death and outcome other than routine or short-term hospital, was observed in 20%.

3.4. Risk of Death and Unfavorable Outcome. A total of 19 variables were studied for their association with outcome in IVM patients (Table 2). The variables were chosen based on statistical significance in the univariate analysis and based on their potential relevance in having an effect on outcome. Overall, mechanical ventilation (OR 20.3 [95%-CI 15.0–27.3]) and ICrH (OR 2.9 [2.3–3.8]) were strongly associated with in-hospital death (Table 2). Unfavorable discharge outcome showed strong positive associations with ventilation (OR 2.8 [2.4–3.2]), ICrH (OR 2.1 [1.8–2.3]), seizure (OR 1.6 [1.5–1.7]), acute ischemic stroke (OR 1.5 [1.4–1.8]), surgery (OR 1.4 [1.2–1.6]), and unruptured ICA-aneurysm (OR 1.4 [1.1–1.7]).

3.5. Hemorrhagic Presentation and Surgery

3.5.1. Hemorrhagic versus Nonhemorrhagic Presentation. Compared with patients with ICrH, patients without bleeds were younger, more frequently women and White, were more often elective admissions, and presented more often with ischemia, seizure, or headache, underwent more endovascular and radiosurgical interventions, and had a shorter length of stay and better outcomes (Table 3/ Figures 2(a) and 2(b)).

3.5.2. Hemorrhagic Presentation: Surgery versus No Surgery. From 6,144 patients with ICrH 12.1% (\( n = 745 \)) underwent surgery. Compared with patient who did not undergo surgery, patients with surgery were less frequently White, but more often Asian, more often elective admissions, had more parenchymal bleeds and ischemia, longer length of stay, and worse outcomes (Table 3/ Figures 2(a) and 2(b)).

3.5.3. Nonhemorrhagic Presentation: Surgery versus No Surgery. From 51,873 patients without ICrH 13.1% (\( n = 6,697 \)) underwent surgery. Compared with patient who did not undergo surgery, patients with surgery were younger, less frequently White or Black, but more often Hispanic, more often elective admissions, had less frequently ischemia or headache, endovascular treatment or radiosurgery, but underwent more often aneurysm clipping, had longer length of stay, and worse outcomes (Table 3/ Figures 2(a) and 2(b)).

3.6. Cost. Hospital charges (Figure 3) increased from an average charge of $32,355 ± 43,442 per admission in 2000/2001 to an average of $51,398 ± 16412 in 2006/2007. The total charge increased from $415,876,303 in 2000/2001 to $843,533,680 in 2006/2007 during this period. This equals an absolute increase of $427,657,377 and a relative increase by 103%.

A total of 23 variables were included to determine the association with hospital charges (Table 4). Major determinants included length of stay, number of procedures, embolization, and surgery (\( r^2 = 0.66; P < 0.001 \)). In a second model only 8 variables were included that revealed similar results as the first model, but included “time” as a major determinant (\( r^2 = 0.62; P < 0.001 \)). The overall cost-to-charge ratio was 0.5.

3.7. Trend Analysis. Over time there was an increase in the number of IVM-related admissions, average age, proportion of women, proportion of acute admissions, and number of diagnoses per patient. Frequencies of cerebral ischemia (stroke and TIA) and headache increased, whereas the incidence of ICrH and seizure showed a downward trend. Except for embolization, all other operative procedures were performed less frequently over time. Although in-hospital death rate remained stable, the proportion of unfavorable discharge outcome increased over time.

3.8. Comparison with Population Estimates. Data from the US Census 2000 showed similar population distribution pattern compared with the NIS IVM sample: North-East 18.3% (versus 19.1%), Midwest 22.1% (versus 22.2%), South 36.4 (versus 34%), and West 23.2% (24.7). The distribution of rural, urban, and urban academic centers were similar across all four US regions (Figure 4). The racial-ethnic distributions in the NIS IVM-sample match the data from the US Census 2000 (Figure 5).

4. Discussion

4.1. Epidemiology and Clinical Features. Based on the average frequency of ICrH of 11% as the primary diagnosis and assuming 50–62% of adult BAVM patients present without hemorrhage initially [3, 11], the crude estimate of “incidental” BAVMs would be approximately 22–27% of the NIS IVM sample, that is, approximately 1600–2000 patients per year. With consideration of multiple admissions—the NIS does not allow the identification of multiple admissions—BAVM-related admissions may be much higher. Among other IVMs than AVMs, cerebral CMs and VMs (often associated with
| Year                  | 2000/2001 | 2002/2003 | 2004/2005 | 2006/2007 | Total          |
|----------------------|-----------|-----------|-----------|-----------|----------------|
| Number of IVM-related admissions | n = 13,500 | n = 14,242 | n = 13,331 | n = 16,977 | 58,051         |
| Total number of admissions | 73,605,206 | 76,024,680 | 77,825,620 | 78,992,164 | 306,447,670    |
| Age, years (SD)       | 48.3 (17.1) | 47.8 (17.4) | 49.2 (17.2) | 50.1 (17.3) | <0.001 48.9 (17.3) |
| Women (%)             | 51.5       | 51.8       | 51.7       | 54.2       | <0.001 52.4    |
| Admission type (%)    |            |            |            |            | <0.001         |
| Emergent              | 42         | 39.7       | 49.5       | 51         | 46             |
| Urgent                | 18.1       | 18.3       | 15.6       | 15.9       | 16.9           |
| Elective              | 39.9       | 41.8       | 34.5       | 32.8       | 37             |
| Emergent and urgent   | 60.1       | 58         | 65.1       | 66.9       | 62.9           |
| Disposition (%)       |            |            |            |            | <0.001         |
| Routine               | 74.7       | 77.5       | 74.1       | 72.8       | 74.7           |
| Short-term hospital   | 5          | 3.7        | 4.1        | 4.6        | 4.4            |
| Another type facility | 13.4       | 11.2       | 11.9       | 13.4       | 12.5           |
| Home health care      | 4.7        | 4.9        | 6.3        | 6.5        | 5.7            |
| Against medical advice| 0.3        | 0.6        | 1.1        | 0.8        | 0.7            |
| Died                  | 1.9        | 2          | 2.4        | 1.8        | 0.005 2        |
| Bad outcome*          | 20.3       | 18.7       | 21.7       | 22.5       | <0.001 20.9    |
| Length of stay, days  | 5.9 (8.2)  | 5.4 (8.3)  | 5.4 (7.2)  | 5.4 (8.8)  | <0.001 5.5 (8.2) |
| Number of diagnoses, any | 4.9 (3.1) | 5.2 (3.3) | 5.9 (3.5) | 6.8 (4.2) | <0.001 5.8 (3.6) |
| Number of procedures, any | 2.0 (2.1) | 1.9 (2.0) | 1.8 (2.0) | 2.0 (2.4) | <0.001 2.0 (2.2) |
| Race                  |            |            |            |            | <0.001         |
| White                 | 69.0       | 67.9       | 69.6       | 64.3       | 67.5           |
| Black                 | 10.9       | 12.1       | 12.1       | 12.4       | 11.9           |
| Hispanic              | 11.9       | 13.0       | 12.0       | 15.6       | 13.2           |
| Asian                 | 4.7        | 3.3        | 3.0        | 3.4        | 3.6            |
| Native American       | 0.3        | 0.3        | 0.3        | 1.1        | 0.5            |
| Other                 | 3.1        | 3.3        | 3.0        | 3.2        | 3.1            |
| Specific diagnosis all ranks |        |            |            |            |                 |
| Any ICrH              | 17.5       | 14.0       | 14.8       | 13.7       | <0.001 14.9    |
| SAH                   | 5          | 4.0        | 4.3        | 4.5        | 0.001 4.4      |
| ICH                   | 11.9       | 9.2        | 9.5        | 8.4        | <0.001 9.7     |
| Other ICrH            | 1.4        | 1.5        | 1.6        | 1.8        | 0.068 1.6      |
| Seizure               | 33.8       | 32.5       | 30.0       | 31.1       | <0.001 31.8    |
| Headache              | 7.1        | 7.8        | 10.1       | 11.7       | <0.001 9.3     |
| Acute ischemic stroke | 5.9        | 6.1        | 7.2        | 7.9        | <0.001 6.8     |
| TIA                   | 2.1        | 2.1        | 2.7        | 3.1        | <0.001 2.5     |
| Primary specific diagnosis only |        |            |            |            |                 |
| Any ICrH              | 72.1       | 71.6       | 66.5       | 65.2       | <0.001 68.6    |
| Seizure               | 12.6       | 9.3        | 11.4       | 9.4        | <0.001 10.6    |
| Headache              | 5.7        | 5.1        | 5.6        | 7.0        | <0.001 5.9     |
| Acute cerebral ischemia| 1.4        | 1.5        | 2.4        | 1.9        | <0.001 1.8     |
| TIA                   | 2.4        | 2.4        | 3.5        | 4.1        | <0.001 3.1     |
| IVM                   | 48.4       | 51.8       | 41.9       | 40.8       | <0.001 45.5    |
| Intracranial ICA aneurysm, unruptured Procedures |        |            |            |            |                 |
| Cerebral angiogram    | 2.5        | 2.7        | 2.8        | 2.7        | 0.305 2.7      |
| Embolization          | ——         | 15.5       | 17.4       | 18.4       | <0.001 13.4    |
Table 1: Continued.

| Year          | 2000/2001 | 2002/2003 | 2004/2005 | 2006/2007 | P   | Total |
|---------------|-----------|-----------|-----------|-----------|-----|-------|
| Number of IVM-related admissions | n = 13,500 | n = 14,242 | n = 13,331 | n = 16,977 |     | 58,051 |
| Surgery       | 14.9      | 12.9      | 11.3      | 12.3      | <0.001 | 12.8  |
| Radiosurgery  | 2.5       | 3.3       | 1.4       | 0.7       | <0.001 | 1.9   |
| Aneurysm clipping | 1.9     | 1.3       | 1.2       | 1.2       | <0.001 | 1.4   |
| Embolization, and surgery | 0.1      | 1.2       | 1.6       | 2.5       | <0.001 | 1.4   |
| No procedure  | 80.1      | 68.6      | 70.8      | 70.2      | <0.001 | 72.2  |
| Mechanical ventilation, all durations | 5.4 | 4.8 | 5.8 | 5.9 | <0.001 | 5.5 |
| ≤96 hours     | 2.4       | 2.3       | 2.4       | 2.0       | 0.057  | 2.3   |
| ≥96 hours     | 2.4       | 2.3       | 2.4       | 2.0       | 0.057  | 2.3   |

*Death, another type facility, or home health care. †11%, misrepresentative figure, likely due to false or not coding. Standard deviation in parenthesis.

Abbreviations: ICrH: intracranial hemorrhage, SAH: subarachnoid hemorrhage, ICH: intracerebral hemorrhage, TIA: transient ischemic attack, IVM: intracranial vascular malformation, ICA: internal carotid artery.

Table 2: Risk of Death and Unfavorable Outcome*

|                | Death                      | OR  | 95%-CI          | P     | Unfavorable Outcome | OR  | 95%-CI          | P     |
|----------------|----------------------------|-----|-----------------|-------|---------------------|-----|-----------------|-------|
| Age            | 1.02 (1.02–1.03)           | <0.001 | 1.04  | (1.04–1.04)       | <0.001 |
| Elective admission | 0.65 (0.47–0.90)       | 0.010  | 0.82  | (0.75–0.90)       | <0.001 |
| Women          | 1.16 (0.93–1.45)           | 0.191  | 1.11  | (1.03–1.20)       | 0.005 |
| Length of stay | 0.96 (0.95–0.97)           | <0.001 | 1.08  | (1.07–1.08)       | <0.001 |
| Number of procedures | 1.13 (1.07–1.19) | <0.001 | 1.06  | (1.03–1.08)       | <0.001 |
| White race     | 1.07 (0.84–1.37)           | 0.585  | 0.99  | (0.90–1.07)       | 0.738 |
| ICrH, any type | 2.93 (2.27–3.80)           | <0.001 | 2.06  | (1.85–2.30)       | <0.001 |
| Seizure        | 1.33 (1.05–1.68)           | 0.020  | 1.59  | (1.46–1.72)       | <0.001 |
| Headache       | 0.25 (0.10–0.59)           | 0.002  | 0.70  | (0.60–0.81)       | <0.001 |
| ICA aneurysm, unruptured | 1.91 (1.08–3.40) | 0.027  | 1.38  | (1.09–1.74)       | 0.007 |
| Acute cerebral ischemia | 0.98 (0.65–1.49) | 0.942  | 1.55  | (1.36–1.76)       | <0.001 |
| Cerebral angiography | 0.27 (0.20–0.37) | <0.001 | 0.62  | (0.56–0.69)       | <0.001 |
| Embolization   | 1.54 (1.00–2.35)           | 0.049  | 0.90  | (0.77–1.04)       | 0.163 |
| Surgery        | 1.04 (0.74–1.46)           | 0.834  | 1.38  | (1.21–1.58)       | <0.001 |
| Radiosurgery   | 0.00 (0.00–1.00)           | 0.994  | 0.50  | (0.31–0.81)       | 0.005 |
| Aneurysm clipping | 0.47 (0.18–1.20)    | 0.115  | 0.44  | (0.31–0.62)       | <0.001 |
| Ventilation    | 20.26 (15.01–27.34)        | <0.001 | 2.77  | (2.37–3.25)       | <0.001 |
| Hospital bed size | 1.13 (1.00–1.29)   | 0.057  | 1.07  | (1.02–1.12)       | 0.002 |
| Hospital location/teaching | 0.94 (0.81–1.09) | 0.397  | 1.07  | (1.01–1.12)       | 0.016 |

*Goodness of fit model summary: Death (Nagelkerke $R^2 = 0.342$), Unfavorable Outcome (Nagelkerke $R^2 = 0.281$).

Abbreviations: 95%-CI: 95% Confidence Interval, ICrH: intracranial hemorrhage, ICA: internal carotid artery.

Each other) are more frequent, but relatively benign diseases that may present with signs of new or old hemorrhage previously left undetected due to lacking symptoms [18, 19]. Vein of Galen malformations are prevalent in childhood and AV fistula mostly present without a bleed [20].

The ICD-9 coding system is not specific in terms of type of congenital cerebrovascular malformation. Thus, the estimate on the incidence and prevalence of IVM subtypes can only be crude. However, our estimate on the average annual detection rate of 2.24 IVMs per 100,000 patient-years is similar to findings from previous population-based studies, such as from Olmsted County in Minnesota [21] and the New York Islands [3], USA, and Scotland [2], UK. Hereby, detection rates for BAVMs range from 1.11–1.34 per 100,000 person-years, for CMs from 0.17–0.57 per 100,000 person-years, for VMs from 0.41–0.44 per 100,000 person-years, for dural AVMs from 0.15–0.16 per 100,000 person-years, and for all IVMs from 1.82–2.3 per 100,000 person-years.

With increasing utilization of brain imaging, such as CT and MRI, more IVMs are found incidentally than before [3, 19]. However, symptoms, including seizure, headache, focal and global neurological deficits, and tinnitus, among others, account for the detection of a significant proportion of
Table 3: Univariate analyses: hemorrhage versus no hemorrhage and surgery versus no surgery.

| N Group number | Hemorrhage (n = 6,144) | No hemorrhage (n = 51,098) | P       |
|----------------|------------------------|-----------------------------|---------|
|                | All                    | Surgery                     | No Surgery | All | Surgery | No Surgery | 1 versus 2 | 1a versus 1b | 2a versus 2b |
| 6,144          |                        | 745                         | 5,399      | 51,098 | 6,697   | 44,401     | <0.001    | 0.094          | <0.001       |
| 1              |                        | 1a                          | 1b         | 2     | 2a      | 2b         | <0.001    | <0.001         | <0.001       |
| Age            | 50.7 (17.1)            | 51.7 (16.6)                 | 50.6 (17.2)| 48.9 (17.3)| 41.6 (13.9)| 50.0 (17.5)| <0.001    | 0.094          | <0.001       |
| Female (%)     | 49.4                   | 47.9                        | 49.6       | 52.8   | 53.8    | 52.7       | <0.001    | 0.404          | 0.092        |
| Race (%)       |                        |                             |            |        |        |            | <0.001    | <0.001         | <0.001       |
| White          | 64.6                   | 58.8                        | 65.3       | 68.2   | 64.9    | 68.6       | <0.001    | <0.001         | <0.001       |
| Black          | 13.5                   | 14.7                        | 13.4       | 11.6   | 8.4     | 12.1       | <0.001    | <0.001         | <0.001       |
| Hispanic       | 13.8                   | 13.9                        | 13.8       | 13.1   | 17.9    | 12.4       | <0.001    | <0.001         | <0.001       |
| Asian          | 4.1                    | 6.4                         | 3.8        | 3.5    | 4.4     | 3.4        | <0.001    | <0.001         | <0.001       |
| Native Americ  | 0.2                    | 0                           | 0.3        | 0.6    | 0.6     | 0.6        | <0.001    | <0.001         | <0.001       |
| Other          | 3.7                    | 6.2                         | 3.4        | 3.1    | 3.8     | 3          | <0.001    | <0.001         | <0.001       |
| Admission (%)  |                        |                             |            |        |        |            | <0.001    | <0.001         | <0.001       |
| Emergent       | 66.7                   | 60.5                        | 67.5       | 43.1   | 10.3    | 47.1       | <0.001    | 0.001          | 0.001        |
| Urgent         | 24.4                   | 28.4                        | 23.8       | 15.9   | 10.9    | 16.5       | <0.001    | 0.001          | <0.001       |
| Elective       | 8.7                    | 11.1                        | 8.3        | 40.8   | 78.8    | 36.2       | <0.001    | 0.078          | <0.001       |
| Emergent and Urgent | 91.1 | 88.9                        | 99.6       | 59     | 21.2    | 63.6       | <0.001    | <0.001         | <0.001       |
| Number of diagnoses | 6.7 (3.5) | 7.5 (3.3) | 6.6 (3.5) | 5.6 (3.6) | 4.2 (2.9) | 5.8 (3.7) | <0.001    | <0.001         | <0.001       |
| Number of procedures | 3 (2.9) | 5.5 (3.1) | 2.6 (2.7) | 1.8 (1.9) | 3.2 (2.3) | 1.6 (1.7) | <0.001    | <0.001         | <0.001       |
| Diagnosis, any (%) |           |                             |            |        |        |            | <0.001    | <0.001         | <0.001       |
| ICH            | 65.4                   | 71.1                        | 64.6       | 0      | 0       | 0          | <0.001    | <0.001         | <0.001       |
| SAH            | 31.3                   | 26.2                        | 32         | 0      | 0       | 0          | <0.001    | 0.002          | <0.001       |
| Other ICrH     | 9.4                    | 12.9                        | 8.9        | 0      | 0       | 0          | <0.001    | <0.001         | <0.001       |
| Acute Ischemia | 4.5                    | 4                           | 2.7        | 7.4    | 1.4     | 8.3        | <0.001    | 0.053          | <0.001       |
| Seizure        | 19.4                   | 17                          | 19.7       | 33.7   | 33.4    | 33.7       | <0.001    | 0.078          | <0.001       |
| Headache       | 4.6                    | 1.5                         | 5          | 10     | 5.7     | 10.6       | <0.001    | <0.001         | <0.001       |
| ICA aneurysm, unruptured | 3.1 | 2.7                         | 3.1        | 2.6    | 2.4     | 2.7        | <0.001    | 0.517          | 0.252        |
| Angiogram      | 50.9                   | 50.7                        | 50.9       | 34.7   | 45.9    | 33.2       | <0.001    | 0.937          | <0.001       |
| Embolization   | 7                      | 8.2                         | 6.9        | 14.3   | 11.6    | 14.7       | <0.001    | 0.213          | <0.001       |
| Surgery        | 12.1                   | —                           | —          | 12.1   | —       | —          | 0.099     | —              | —             |
| Radiosurgery   | 0.1                    | 0                           | 0.1        | 2.2    | 0.3     | 2.5        | <0.001    | 0.405          | <0.001       |
| Aneurysm clipping | 4.2 | 2.9                         | 4.4        | 1      | 1.7     | 0.9        | <0.001    | 0.065          | <0.001       |
| Ventilation, all durations | 23.2 | 36.1                         | 21.4       | 2.7    | 4.9     | 2.5        | <0.001    | <0.001         | <0.001       |
| Ventilation >95 h | 11 | 22.6                      | 9.3         | 0.9    | 2.4     | 0.7        | <0.001    | <0.001         | <0.001       |
| Length of stay (d) | 10.4 (12.9) | 16.4 (11.5) | 9.6 (12.9) | 4.6 (5.8) | 6.8 (6.4) | 4.3 (5.7) | <0.001    | <0.001         | <0.001       |
Table 3: Continued.

| Group number | Hemorrhage ($n = 6,144$) | No hemorrhage ($n = 51,098$) | $P$ |
|--------------|--------------------------|-----------------------------|-----|
|              | All (Surgery) | No Surgery | All (Surgery) | No Surgery | 1 versus 2 | 1a versus 1b | 2a versus 2b |
| 1            | 745 | 5,399 | 2 | 6,697 | 44,401 | <0.001 | <0.001 | <0.001 |
| 1a           | 31.5 | 46.2 | 79.3 | 44.4 | 79.7 | 79.3 | <0.001 | <0.001 | <0.001 |
| 1b           | 46.2 | 10.2 | 3.1 | 25.1 | 1.1 | 0.9 | <0.001 | <0.001 | <0.001 |
| 2            | 27.6 | 13.6 | 0.6 | 25.1 | 4.7 | 5.8 | <0.001 | <0.001 | <0.001 |
| 2a           | 3.9 | 3.1 | 0.6 | 5.2 | 4.7 | 5.8 | <0.001 | <0.001 | <0.001 |
| 2b           | 10.2 | 5.7 | 13.7 | 5.7 | 4.7 | 5.8 | <0.001 | <0.001 | <0.001 |
| Outcome (%)  | 42.2 | 39.2 | 16.8 | 64.5 | 19.5 | 16.5 | <0.001 | <0.001 | <0.001 |
| Routine discharge | 71,151 (90,787) | 14,0034 (123,099) | 14,0034 (123,099) | 71,151 (90,787) | <0.001 | <0.001 | <0.001 |
| Short-term hospital | 33.9 | 30.7 | 16.8 | 34.8 | 19.4 | 24.3 | <0.001 | <0.001 | <0.001 |
| Other type facility | 18.3 | 15.4 | 9.8 | 17.8 | 12.9 | 18.4 | <0.001 | <0.001 | <0.001 |
| Home health care | 2.7 | 4.2 | 1.8 | 4.2 | 1.1 | 1 | <0.001 | <0.001 | <0.001 |
| Death | 5.2 | 3.4 | 1.7 | 5.2 | 1.7 | 1 | <0.001 | <0.001 | <0.001 |
| Unfavorable outcome | 42.2 | 39.2 | 16.8 | 64.5 | 19.5 | 16.5 | <0.001 | <0.001 | <0.001 |
| Charges mean ($) | 71,151 (90,787) | 14,0034 (123,099) | 14,0034 (123,099) | 71,151 (90,787) | <0.001 | <0.001 | <0.001 |
| Charges sum ($) | 414.8 Mill | 102.6 Mill | 312.3 Mill | 1,717.4 Mill | <0.001 | <0.001 | <0.001 |
| Hospital Characteristics | 539 Mill | 1,380 Mill | 539 Mill | 1,380 Mill | <0.001 | <0.001 | <0.001 |
| Bed Size | 9.2 | 0.9 | 1.1 | 9.2 | 0.9 | 1.1 | <0.001 | <0.001 | <0.001 |
| Small | 39.4 | 39.3 | 40.1 | 40.4 | 40.1 | 40.1 | <0.001 | <0.001 | <0.001 |
| Medium | 26.2 | 25.4 | 28 | 26.1 | 28.2 | 28.2 | <0.001 | <0.001 | <0.001 |
| Large | 34.3 | 35.3 | 31.9 | 33.6 | 31.7 | 31.7 | <0.001 | <0.001 | <0.001 |
| Location/Teaching | 0.265 | 0.265 | 0.265 | 0.265 | <0.001 | <0.001 | <0.001 |
| Rural | 43.6 | 42.5 | 42.4 | 43.4 | 42.2 | 42.2 | <0.001 | <0.001 | <0.001 |
| Urban Non-Teaching | 40.1 | 41.7 | 40.9 | 41.8 | 40.7 | 40.7 | <0.001 | <0.001 | <0.001 |
| Urban Teaching | 16.3 | 15.9 | 16.7 | 14.8 | 17 | 17 | <0.001 | <0.001 | <0.001 |
| Hospital Region | 0.088 | 0.088 | 0.088 | 0.088 | <0.001 | <0.001 | <0.001 |
| NE | 18.2 | 18.2 | 19.4 | 14.7 | 20.1 | 20.1 | <0.001 | <0.001 | <0.001 |
| NW/NC | 22 | 22.1 | 22.4 | 21.3 | 23.3 | 23.3 | <0.001 | <0.001 | <0.001 |
| S | 33.9 | 34.8 | 33.9 | 33.1 | 34 | 34 | <0.001 | <0.001 | <0.001 |
| W | 25.8 | 24.9 | 24.3 | 36.2 | 22.7 | 22.7 | <0.001 | <0.001 | <0.001 |

Standard deviation in parenthesis.
Abbreviations: ICrH: intracranial hemorrhage, SAH: subarachnoid hemorrhage, ICA: internal carotid artery.
BAVMs (79–85%), CMs (40–43%), VMs (7–14%), and dural AV fistulas (85–100%) [2, 21]. Prospective studies found that patients with BAVMs presented with ICrH, seizure, headache, and focal neurological deficits in 38–71%, 24–40%, 5–14%, and 5–20%, respectively [22–25]. When our findings on the frequency of ICrH (11%), seizure (6%), headache (2%), and cerebral ischemia (5%) are translated into relative proportions, they result in 46%, 25%, 8%, and 21%, respectively.

4.2. Treatment and Outcome. The multivariate analyses showed that mechanical ventilation had the highest association with death or unfavorable outcome. A plausible way of interpretation is that ICrH and surgery, both with negative associations with outcome, would necessitate intensive medical care like for any patient in a critical condition. However, seizure, ischemic stroke, and unruptured aneurysm were also significantly associated with unfavorable outcome some of which might occur concurrently with hemorrhage, but may also be unrelated to it.

The clinical outcome after BAVM-related hemorrhage appears to be more favorable compared with the outcome after primary intracerebral hemorrhage (ICH) [8, 9]. Death rates following BAVM-related bleeds range between 0–11% (versus 50% after ICH) and short- (30 days) and medium-term (one year) functional outcome has been observed to be relatively favorable with a median NIHSS score of 1 (versus median NIHSS of 12) and median Rankin Scale (RS) score of 2 (versus median RS of 6), respectively.
Table 4: Determinants of hospital charges.

(a)

|                          | Model 1          |  | Model 2          |  |
|--------------------------|------------------|---|------------------|---|
|                          | Unstd. Coefficients $B$ | Standard Error | Std. coefficients $\beta$ | $t$ | $P$ | Unstd. Coefficients $B$ | Standard Error | Std. coefficients $\beta$ | $t$ | $P$ |
| Age (y)                  | 61.48            | 11.49 | 0.0200 | 5.3514 | 0.00000 | 3412.81 | 22.53 | 0.4535 | 151.5009 | 0.00000 |
| Elective admission       | 1763.74          | 424.92 | 0.0160 | 4.1508 | 0.00003 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| In-hospital death        | 12044.56         | 1339.92 | 0.0317 | 8.9890 | 0.00000 | 5677.02 | 137.73 | 0.1095 | 41.2199 | 0.00000 |
| Women                    | −669.94          | 351.65 | −0.0063 | −1.9052 | 0.05677 | −1.9052 | 0.05677 | 2804.75 | 931.44 | 0.0182 | 3.0112 | 0.00260 |
| Length of stay (d)       | 3613.12          | 28.99 | 0.5026 | 124.6288 | 0.00000 | 3412.81 | 22.53 | 0.4535 | 151.5009 | 0.00000 |
| # Diagnoses              | −287.82          | 61.42 | −0.0199 | −4.6863 | 0.00000 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| # Procedures             | 7049.92          | 118.25 | 0.2800 | 59.6181 | 0.00000 | 5677.02 | 137.73 | 0.1095 | 41.2199 | 0.00000 |
| Time (year)              | 6169.46          | 232.79 | 0.5026 | 26.5024 | 0.00000 | 5677.02 | 137.73 | 0.1095 | 41.2199 | 0.00000 |
| Median income            | 847.15           | 156.29 | 0.0124 | 3.1800 | 0.00147 | 5677.02 | 137.73 | 0.1095 | 41.2199 | 0.00000 |
| ICrH                     | 1300.84          | 1135.07 | 0.0039 | 1.1460 | 0.25179 | 2804.75 | 931.44 | 0.0182 | 3.0112 | 0.00260 |
| ICA aneurysm, unruptured | 1300.84          | 1135.07 | 0.0039 | 1.1460 | 0.25179 | 2804.75 | 931.44 | 0.0182 | 3.0112 | 0.00260 |
| Acute ischemia           | 530.73           | 693.29 | 0.0026 | 0.7655 | 0.44397 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| Seizure                  | −60.35           | 414.97 | −0.0005 | −0.1454 | 0.88438 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| Headache                 | 1414.91          | 636.16 | 0.0082 | 2.2241 | 0.02615 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| Angiography              | 1372.53          | 431.61 | 0.0124 | 3.1800 | 0.00147 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| Embolization             | 29192.74         | 534.78 | 0.2086 | 54.5888 | 0.00000 | 29502.47 | 47.37 | 0.1707 | 62.2773 | 0.00000 |
| IVM surgery              | 26550.75         | 608.40 | 0.1564 | 43.6403 | 0.00000 | 27449.01 | 48.44 | 0.1553 | 56.1973 | 0.00000 |
| Radiosurgery             | 27182.37         | 1354.84 | 0.0682 | 20.0632 | 0.00000 | 16798.46 | 112.82 | 0.0397 | 14.9609 | 0.00000 |
| Aneurysm clip            | 27896.46         | 1678.19 | 0.0573 | 16.6230 | 0.00000 | 17164.04 | 134.84 | 0.0338 | 12.7914 | 0.00000 |
| Ventilation              | 26550.75         | 608.40 | 0.1564 | 43.6403 | 0.00000 | 27449.01 | 48.44 | 0.1553 | 56.1973 | 0.00000 |
| ICrH primary diagn.      | 3325.46          | 1054.94 | 0.0187 | 3.1523 | 0.00162 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| Seizure primary diagnosis| 1473.41          | 787.55 | 0.0068 | 1.8709 | 0.06137 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| Headache primary diagnosis| 921.68          | 1334.31 | 0.0025 | 0.6908 | 0.48972 | 8824.37 | 92.78 | 0.3215 | 95.1101 | 0.00000 |
| Constant                 | −26640.78        | 1063.46 | −25.0510 | −17986.64 | 416.53 | −43.1820 | 0.00000 |

(b)

|                          | Adjusted $R^2$ | df1 | df2 | Sig. $F$ Change | Durbin-Watson |
|--------------------------|----------------|-----|-----|-----------------|---------------|
| Model 1                  | 0.6648         | 23  | 31610 | 0.0000          | 0.3258        |
| Model 2                  | 0.6161         | 8   | 56205 | 0.0000          | 0.3172        |

Abbreviations: Unstd.: unstandardized, Std.: standardized, #: number of, ICrH: intracranial hemorrhage, ICA: internal carotid artery, IVM: intracranial vascular malformation.

Because of the negative associations with outcome and because it is difficult to tell which IVM subtype was treated in our sample, we performed a more thorough analysis based on the presence of ICrH (primary diagnosis) and on whether surgery was performed or not. Overall, 9% of the patients with ICrH died and 42% had unfavorable discharge outcome. Among patients without hemorrhage 0.9% died and 17% had unfavorable outcome. The odds for death and bad outcome were highest with the presence of ICrH. Interestingly, surgery was linked to higher odds for death in patients with bleeds and to higher odds for bad outcome in both, bled and unbled patients. Whether this indicates that the most severely affected patients and challenging IVMs are selected for surgery or whether surgery itself poses a greater risk to the patient, regardless of the integrity of the IVM, cannot be derived from our data.
This may simply reflect the fact that surgery has a known complication and risk profile that may be offset by a decrease in potential morbidity and mortality from a treated IVM over the remaining life of the individual. Such discounting of the beneficial effects of surgical excision of IVMs in an effort to qualify the finding of surgery as an independent predictor of bad outcome and death is beyond the scope of this analysis. The data may, however, in part reflect the current heterogeneous center-specific management pattern of, specifically, BAVMs which remains a challenge and is subject to ongoing studies [12, 26]. Ongoing and future studies may and ought to give better insights to the rate and degree of recovery from invasive therapies in unbled patients in order to distinguish temporary from permanent functional deficits. It is, nevertheless, important to note that among patients admitted to US hospitals with the diagnoses of an IVM and ICrH, almost 1/10th will die and 2/5th will either die or be discharged to long-term health care facilities or home with home health care. Even more striking is the fact that among patients with the diagnosis of an IVM and without the presence of ICrH, only 1% will die, but still almost 1/6th will either die or be discharged with specialized medical care. Overall, 1/5th of all IVM-related admissions will either die or be discharged with long-term care.

4.3. Trend. The comparison of our results with the US consensus data from 2000 suggests that IVMs are equally distributed among racial and ethnic groups and gender groups. It is interesting, however, that the average age increased from 48 ± 17 years to 50 ± 17 years over the study period (8 years). Assuming stable IVM detection rates [2–4] this could reflect general aging of the US population and mean that IVMs are now detected later in life. Perhaps, the overall improvement of vascular preventive management, such as treatment of hypertension, smoking cessation, and healthier life style, allows IVMs to remain undetected for a longer period of time. The decrease in the rate of ICrH may be an indicator for such improvements while the rates for seizure and headache remained relatively stable. However, the rate of cerebral ischemic events increased which might be an age and gender effect outweighing the effects of preventive measures. Also, more patients with IVMs present now in an emergent or urgent setting, that is, less electively. This may indicate that while IVMs remain longer silent, once they become symptomatic the clinical picture is relatively dramatic. The trend in the management of IVMs, however, is less invasive in diagnosis (less frequent cerebral angiograms) and therapy (less frequent surgery, but more endovascular therapy). However, radiation therapy also decreased over time. The latter might be due to the increasing shift of radiation therapy into the outpatient setting which is not part of the NIS.

The cost of inpatient IVM management in the US doubled over the 8 years from approximately $200 million in years 2000/2001 to $400 million in years 2006/2007. This is a true increase in cost as the cost-to-charge ratio remained stable at approximately 0.5. Additional factors significantly associated with charges include length of stay, number of procedures, and the main procedures, surgery, and endovascular therapy. In aggregate, the management of non-hemorrhagic patients (primary diagnosis only) accounted for 80% ($1.7 billion) of the total charges over the study period. With an average of almost $300 million of inpatient charges per year, the management of IVMs has economic significance in public health. Not included are costs from the outpatient setting and lost productivity [27].

4.4. Limitations. The main limitation is the fact that the ICD-9 coding system summarizes all IVMs into a single code. It is therefore difficult, if not impossible, to distinguish between IVM subtypes. To alleviate this limitation we performed further selections based on published epidemiological and clinical data (frequency, clinical presentation, and ICrH) and by focusing on the primary diagnostic code when analyzing presenting symptoms. In terms of the design, this study is primarily a cross-sectional study. The main disadvantage is that the results can provide only a “snapshot in time” of IVMs and its management. This design is not ideally suited for answering questions related to disease process or for revealing causal relationships between diseases. Second, our study also has characteristics of a case-control study, albeit unmatched, as we compare groups with and without hemorrhage and groups with and without surgery with each other. Other limitations include unidentifiable multiple admissions, incomplete clinical and anatomical data, for example, severity of symptoms, angioarchitecture, laboratory and imaging data, and unknown magnitude of misclassifications. Finally, because the NIS sample represents nationwide inpatient treatment, it may not reflect the true incidence or prevalence of IVMs in the general population.

However, there are also unique advantages of analyzing the NIS, a source with a large number of cases resulting in an impressive database with 6–8 million admissions per year and with its wealth of information. In addition, because of the representative nature of the NIS the “snapshot in time” becomes “the big picture” for USA hospital management of medical conditions which may give unique insides into rare diseases such as IVMs. NIS data is also well suited for hypothesis generation, especially with trend data, that certainly requires proof in well-designed prospective and longitudinal studies. The introduction of ICD-10 will allow better differentiation between the various IVM subtypes.

5. Conclusions

IVMs are infrequent, equally prevalent among racial-ethnic, and gender groups and present in 1/6 patients with some form of ICrH. Overall, seizure is the dominant comorbid diagnosis (1/3 patients). IVMs are now increasingly detected later in life. The short-term outcome of IVM inpatient care has not markedly changed over almost a decade, resulting in death or discharge into specialized care in 1/5 patients.

Conflict of Interests

All authors declare that they have no relevant conflicts of interest or financial interests to disclose. J. Pile-Spellman
is member of the steering committee of the NIH-funded ARUBA trial.

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