

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 pre-surgical 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

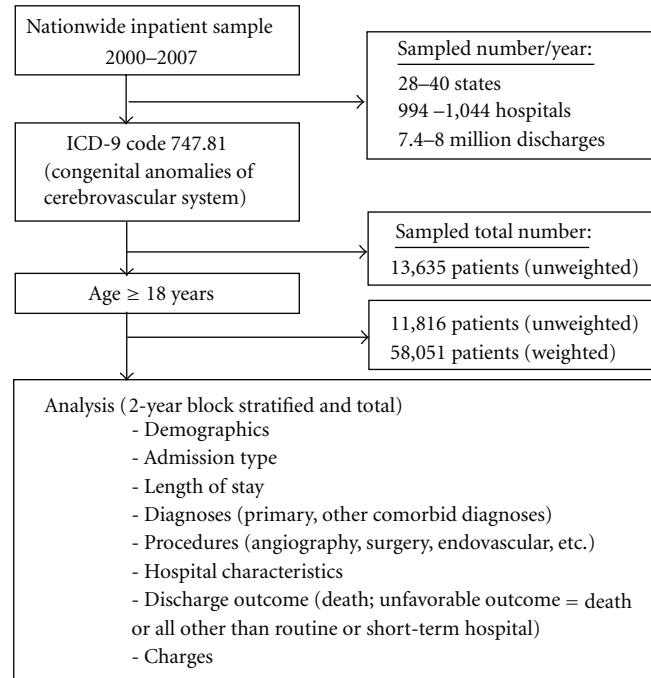


FIGURE 1: Selection flow chart.

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 (χ^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 $\$32,355 \pm 43,442$ per admission in 2000/2001 to an average of $\$51,398 \pm 16,412$ 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

TABLE 1: Univariate statistics.

Year	2000/2001	2002/2003	2004/2005	2006/2007	<i>P</i>	Total
Number of IVM-related admissions	<i>n</i> = 13,500	<i>n</i> = 14,242	<i>n</i> = 13,331	<i>n</i> = 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	72.1	71.6	66.5	65.2	<0.001	68.6
Any ICrH	12.6	9.3	11.4	9.4	<0.001	10.6
Seizure	5.7	5.1	5.6	7.0	<0.001	5.9
Headache	1.4	1.5	2.4	1.9	<0.001	1.8
Acute cerebral ischemia	2.4	2.4	3.5	4.1	<0.001	3.1
TIA	1.6	1.5	1.7	2.0	0.004	1.7
IVM	48.4	51.8	41.9	40.8	<0.001	45.5
Intracranial ICA aneurysm, unruptured	2.5	2.7	2.8	2.7	0.305	2.7
Procedures						
Cerebral angiogram	39.7	38.8	34.8	34.9	<0.001	37.0
Embolization	— [†]	15.5	17.4	18.4	<0.001	13.4

TABLE 1: Continued.

Year	2000/2001	2002/2003	2004/2005	2006/2007	<i>P</i>	Total
Number of IVM-related admissions	<i>n</i> = 13,500	<i>n</i> = 14,242	<i>n</i> = 13,331	<i>n</i> = 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	3.2	2.5	3.4	3.9	<0.001	3.3
≥96 hours	2.4	2.3	2.4	2.0	0.057	2.3

* Death, another type facility, or home health care. †1%, 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			Unfavorable Outcome		
	OR	95%-CI	<i>P</i>	OR	95%-CI	<i>P</i>
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	—	0.994	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	No Surgery	All	No Surgery	1 versus 2	1a versus 1b	2a versus 2b
	6,144	5,399	51,098	44,401			
Age	50.7 (17.1)	51.7 (16.6)	48.9 (17.3)	50.6 (17.5)	<0.001	0.094	<0.001
Female (%)	49.4	47.9	52.8	52.7	<0.001	0.404	0.092
Race (%)					<0.001	<0.001	<0.001
White	64.6	58.8	68.2	68.6			
Black	13.5	14.7	11.6	12.1			
Hispanic	13.8	13.9	13.1	12.4			
Asian	4.1	6.4	3.5	3.4			
Native Americ	0.2	0	0.6	0.6			
Other	3.7	6.2	3.1	3			
Admission (%)					<0.001	0.001	0.001
Emergent	66.7	60.5	43.1	47.1			
Urgent	24.4	28.4	15.9	16.5			
Elective	8.7	11.1	40.8	36.2			
Emergent and Urgent	91.1	88.9	59	63.6			
Number of diagnoses	6.7 (3.5)	7.5 (3.3)	5.6 (3.6)	5.8 (3.7)	<0.001	<0.001	<0.001
Number of procedures	3 (2.9)	5.5 (3.1)	1.8 (1.9)	1.6 (1.7)	<0.001	<0.001	<0.001
Diagnosis, any (%)							
ICH	65.4	71.1	0	0	<0.001	<0.001	<0.001
SAH	31.3	26.2	0	0	<0.001	0.002	<0.001
Other ICrH	9.4	12.9	0	0	<0.001	0.001	<0.001
Acute Ischemia	4.5	4	7.4	8.3	<0.001	0.053	<0.001
Seizure	19.4	17	33.7	33.7	<0.001	0.078	0.681
Headache	4.6	1.5	10	10.6	<0.001	<0.001	<0.001
ICA aneurysm, unruptured	3.1	2.7	2.6	2.7	<0.001	0.517	0.252
Angiogram	50.9	50.7	34.7	33.2	<0.001	0.937	<0.001
Embolization	7	8.2	14.3	14.7	<0.001	0.213	<0.001
Surgery	12.1	—	12.1	—	0.099	—	—
radiosurgery	0.1	0	2.2	2.5	<0.001	0.405	<0.001
Aneurysm clipping	4.2	2.9	1	0.9	<0.001	0.065	<0.001
Ventilation, all durations	23.2	36.1	2.7	2.5	<0.001	<0.001	<0.001
Ventilation >95 h	11	22.6	0.9	0.7	<0.001	<0.001	<0.001
Length of stay (d)	10.4 (12.9)	16.4 (11.5)	4.6 (5.8)	4.3 (5.7)	<0.001	<0.001	<0.001

TABLE 3: Continued.

N Group number	Hemorrhage (n = 6,144)		No hemorrhage (n = 51,098)				P	
	All 6,144	Surgery 745	No Surgery 5,399	All 51,098	Surgery 6,697	No Surgery 44,401	1 versus 2	1a versus 1b 2a versus 2b
	1	1a	1b	2	2a	2b		
Outcome (%)							<0.001	<0.001
Routine discharge	44.4	31.5	46.2	79.3	79.7	79.3		<0.001
Short-term hospital	12.4	3.9	13.6	3.1	0.6	3.4		
Other type facility	27.6	45.6	25.1	10.2	13.7	9.8		
Home health care	5.4	7.1	5.2	5.7	4.7	5.8		
Death	9.2	11.8	8.9	0.9	1.1	0.9		
Unfavorable outcome	42.2	64.5	39.2	16.8	19.5	16.5		
Charges mean (\$)	71,151 (90,787)	14,0034 (123,099)	61,256 (80,452)	35,792 (46,033)	77,846 (68,618)	30,090 (38,675)		<0.001
Charges sum (\$)	414.8 Mill	102.6 Mill	312.3 Mill	1,717.4 Mill	539 Mill	1,380 Mill		
Hospital Characteristics								
Bed Size								
Small	39.4	40.3	39.3	40.1	40.4	40.1	0.01	<0.001
Medium	26.2	32.4	25.4	28	26.1	28.2		
Large	34.3	27.4	35.3	31.9	33.6	31.7		
Location/Teaching								
Rural	43.6	51.8	42.5	42.4	43.4	42.2	0.265	<0.001
Urban Non-Teaching	40.1	29.1	41.7	40.9	41.8	40.7		
Urban Teaching	16.3	19.1	15.9	16.7	14.8	17		
Hospital Region								
NE	18.2	18.5	18.2	19.4	14.7	20.1	0.088	<0.001
NW/NC	22	21.3	22.1	22.4	16	23.3		
S	33.9	27.6	34.8	33.9	33.1	34		
W	25.8	32.7	24.9	24.3	36.2	22.7		

Standard deviation in parenthesis.
Abbreviations: ICRH: intracranial hemorrhage, SAH: subarachnoid hemorrhage, ICA: internal carotid artery.

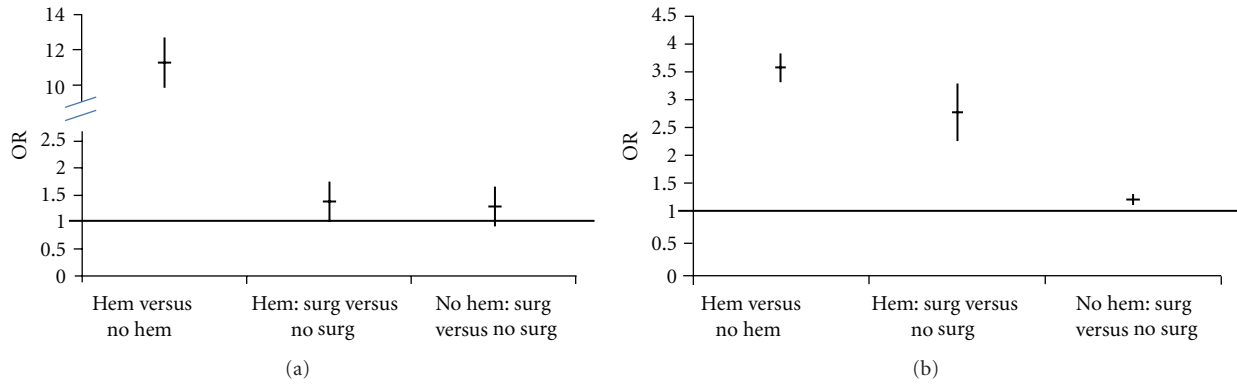


FIGURE 2: (a) Risk of death. (b) Risk of unfavorable outcome.

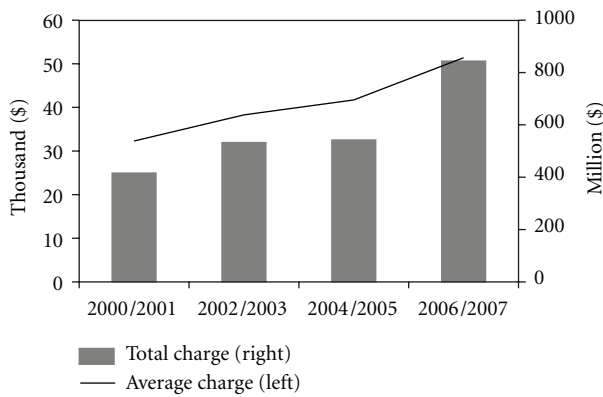


FIGURE 3: Cost of IVM treatment.

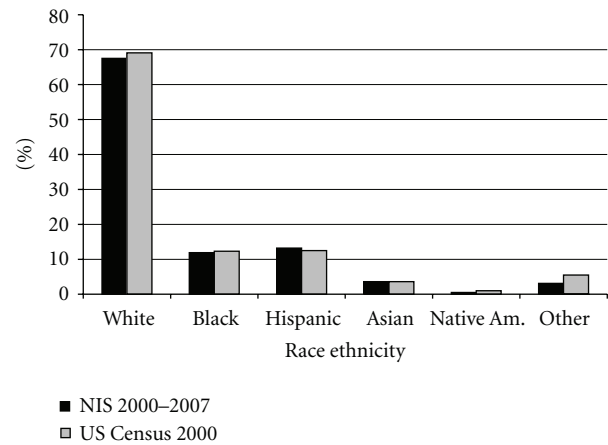


FIGURE 5: Racial and ethnic distribution.

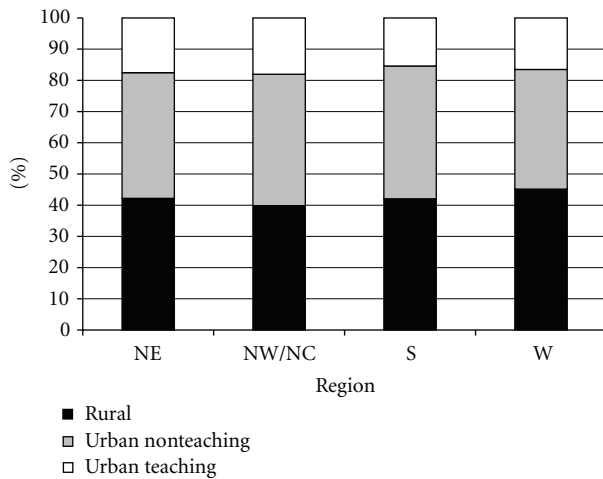


FIGURE 4: US geographic distribution of different types of hospitals in the NIS IVM sample.

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 <i>B</i>	Standard Error	Std. coefficients β	<i>t</i>	<i>P</i>	Unstd. Coefficients <i>B</i>	Standard Error	Std. coefficients β	<i>t</i>	<i>P</i>
Age (y)	61.48	11.49	0.0200	5.3514	0.00000					
Elective admission	1763.74	424.92	0.0160	4.1508	0.00003					
In-hospital death	12044.56	1339.92	0.0317	8.9890	0.00000					
Women	-669.94	351.65	-0.0063	-1.9052	0.05677					
Length of stay (<i>d</i>)	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					
# Procedures	7049.92	118.25	0.2800	59.6181	0.00000	8824.37	92.78	0.3215	95.1101	0.00000
Time (year)	6169.46	232.79	0.0888	26.5024	0.00000	5677.02	137.73	0.1095	41.2199	0.00000
Median income	847.15	156.29	0.0177	5.4205	0.00000					
ICrH	2804.75	931.44	0.0182	3.0112	0.00260					
ICA aneurysm, unruptured	1300.84	1135.07	0.0039	1.1460	0.25179					
Acute ischemia	530.73	693.29	0.0026	0.7655	0.44397					
Seizure	-60.35	414.97	-0.0005	-0.1454	0.88438					
Headache	1414.91	636.16	0.0082	2.2241	0.02615					
Angiography	1372.53	431.61	0.0124	3.1800	0.00147					
Embolization	29192.74	534.78	0.2086	54.5888	0.00000	29502.47	473.73	0.1707	62.2773	0.00000
IVM surgery	26550.75	608.40	0.1564	43.6403	0.00000	27449.01	488.44	0.1553	56.1973	0.00000
Radiosurgery	27182.37	1354.84	0.0682	20.0632	0.00000	16798.46	1122.82	0.0397	14.9609	0.00000
Aneurysm clip	27896.46	1678.19	0.0573	16.6230	0.00000	17164.04	1341.84	0.0338	12.7914	0.00000
Ventilation	12209.90	933.97	0.0518	13.0731	0.00000					
ICrH primary diagn.	3325.46	1054.94	0.0187	3.1523	0.00162					
Seizure primary diagnosis	1473.41	787.55	0.0068	1.8709	0.06137					
Headache primary diagnosis	921.68	1334.31	0.0025	0.6908	0.48972					
Constant	-26640.78	1063.46		-25.0510	0.00000	-17986.64	416.53		-43.1820	0.00000

(b)

	Adjusted <i>R</i> square	df1	df2	Sig. <i>F</i> 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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