Longitudinal Risk of Intracranial Hemorrhage in Patients With Arteriovenous Malformation of the Brain Within a Defined Population

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Background and Purpose—Accurate estimates for risk and rates of intracranial hemorrhage (ICH) in the natural course of patients harboring brain arteriovenous malformation (BAVM) are needed to provide a quantitative basis for planning clinical trials to evaluate interventional strategies and to help guide practice management.

Methods—We identified patients with BAVM at the Kaiser Permanente Northern California health maintenance organization and documented their clinical course. The influences of age at diagnosis, gender, race–ethnicity, ICH at presentation, venous draining pattern, and BAVM size on ICH subsequent to presentation were studied using the multivariate Cox proportional hazards model and Kaplan–Meier curves.

Results—We identified 790 patients with BAVM (51% female; 63% white; mean age ± SD at diagnosis: 38 ± 19 years) between 1961 and 2001. Patients who presented with ICH experienced a higher rate of subsequent ICH than those who presented without ICH under multivariate analysis (hazard ratio, 3.6; 95% CI, 1.1 to 11.9; \( P = 0.032 \)). The effect was similar across race–ethnicity and gender. This difference in ICH rates was greatest in the first year (7% versus 3% per year) and converged over time. The effect of subsequent ICH on functional status was similar to that of the initial ICH.

Conclusions—Presentation with ICH was the most important predictor of future ICH, confirming previous studies. Future ICH had similar impact on functional outcome as incident ICH. Intervention to prevent ICH would be of potentially greater benefit to patients presenting with ICH, although the advantage decreases over time. (Stroke. 2004;35:1697-1702.)

Key Words: cerebral hemorrhage ▪ vascular malformations ▪ epidemiology

Brain arteriovenous malformations (BAVMs) are an important cause of hemorrhagic stroke in young adults.1–4 Treatment decisions can be challenging because of expensive complex treatment (resection, embolization, radiosurgery) and a relative lack of unbiased natural history data.3,4 Accurate estimates for risk and rates of ICH in the natural course of patients harboring BAVM are needed to provide a quantitative basis for planning clinical trials to evaluate interventional strategies and to help guide practice management.

A controversy exists concerning what determines the risk of new hemorrhage if the lesion is left untreated.5,6 A primary unresolved issue is whether clinical presentation with intracranial hemorrhage (ICH) increases the risk of subsequent hemorrhage6–7 or does not affect future bleeding risk.5,9

Our hypothesis was that initial clinical presentation with ICH is associated with a higher rate of subsequent ICH in the natural course before any treatment is undertaken. We present data obtained from a large, community-based, metropolitan health maintenance organization (HMO) that, compared with earlier reports, is less encumbered by selection bias inherent in pure tertiary care patient samples. Additionally, we examine an index of functional outcome from subsequent ICH. These more widely generalizable data confirm earlier reports and make it possible to carefully balance the risks of intervention with conservative medical management.

Patients and Methods

We identified patients with BAVM at Kaiser Permanente Northern California (KPNC) and documented their clinical course using a multimodal approach using several databases from inpatient and outpatient services, radiology reports, and chart review. KPNC is an HMO currently with \( \sim 3.3 \) million members in a 14-county region. It covers a population representative of the sociodemographic characteristics of the Bay Area, but underrepresents residents at both extremes of the socioeconomic continuum.10
TABLE 1. Patient and BAVM Characteristics and Univariate Risk of Subsequent Hemorrhage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Sample</th>
<th>Mean±SD</th>
<th>HR*</th>
<th>95% CI</th>
<th>N (%) With Attribute</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>790</td>
<td>37±20</td>
<td>1.0†</td>
<td>0.8–1.1</td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>BAVM size, maximum dimension (cm)</td>
<td>253</td>
<td>3.2±1.6</td>
<td>1.7‡</td>
<td>0.7–3.9</td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Female gender</td>
<td>772</td>
<td>0.7</td>
<td>0.4–1.1</td>
<td>390 (51)</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>733</td>
<td>1.0</td>
<td>0.6–1.8</td>
<td>230 (31)</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>ICH at presentation</td>
<td>790</td>
<td>2.5</td>
<td>1.5–4.0</td>
<td>367 (46)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Exclusively deep drainage</td>
<td>477</td>
<td>1.8</td>
<td>0.9–3.5</td>
<td>89 (20)</td>
<td></td>
<td>0.07</td>
</tr>
</tbody>
</table>

*HR indicates hazard rate ratio.
†HR estimate for 10 year increment of age at diagnosis.
‡HR estimate for BAVM size small (<3 cm) vs large (≥3 cm).

Ascertainment included an initial screen using ICD-9 code 747.81 to identify all diagnoses of intracranial vascular malformation, which includes BAVM. We searched KPNC’s inpatient admissions and outpatient care databases. The ICD-9 codes were assigned by coders based on diagnostic notes recorded by physicians during the encounter in the emergency room, outpatient clinic, or hospital admission (including an extramural claims database). Unique identifiers prevented recounting from multiple patient visits.

Beginning with calendar year 1998, complete text reports for all radiological procedures were available. The radiology text files were searched using CPT-4 codes for various neuroradiological procedures and screened for various permutations of specified text strings germane to BAVM, arterial-venous malformation, angioma, etc.

The initial visit for each patient was taken as the time of index date, ie, detection of a case as a study patient from one of the various sources. A trained medical records analyst (MRA) generated a list of all the encounters after the index date and the respective sites for medical care. In cases in which date of diagnosis preceded the index date, the MRA reviewed the records with the first mention of BAVM and all subsequent encounters. Using a close-ended data collection sheet, the MRA reviewed photocopies of initial evaluation, follow-up, and treatment for BAVM in the patient records. Lesion size and morphological data were taken from either progress notes or radiology reports.

The abstracts were reviewed by 1 or more of the study physicians (V.S., W.L.Y., S.C.J.) to determine or confirm the underlying diagnosis. A standardized definition was used as previously described:11 an abnormal tangle of vessels that results in arteriovenous shunting, excluding vein of Galen AVM, caver nous malformations, anomalous venous drainage, ruptured arterial aneurysms, dural arteriovenous fistulae, venous malformations, venous varices, or any of the other rarer types of cerebrovascular anomalies. The diagnosis of BAVM was based on information from multiple sources including clinical history, neuroimaging, and, in a few cases, pathology.

The rate of ICH in the subsequent period after BAVM diagnosis, before any intervention, was assessed using survival analysis. The period at risk was defined from the date of first BAVM diagnosis to the date of an event, ie, onset of (first subsequent) ICH, or censoring because of either initiation of first BAVM treatment (surgery, embolization, or radiosurgery) or loss to follow-up (using date of last available follow-up). Cases were censored at first treatment to account for any possible change in natural history risk incurred by intervention for BAVM.

Patient and BAVM characteristics examined included age at diagnosis, gender, race–ethnicity (white versus nonwhite), ICH at presentation (ICH versus no ICH), venous drainage pattern (exclusively deep versus other), and BAVM size (largest dimension <3 cm versus ≥3 cm). Because morphological characteristics had to be abstracted from the medical record text, only deep venous drainage and size were chosen, which are components of the Spetzler–Martin surgical risk scoring system.12 All variables were coded following published standardized guidelines.11

The respective associations between these variables and subsequent ICH were compared using univariate and multivariate Cox proportional hazards models. Stratified analyses were performed to assess statistical interaction by age, gender, and race–ethnicity (white versus nonwhite).

In constructing the multivariate model, we began by including all selected variables into a full model. In a backward stepwise approach, individual variables were subsequently removed from the model singly or in combination to determine the most parsimonious model. Cumulative rate of ICH was displayed using Kaplan–Meier curves. Differences between hemorrhage-free survival for patients who presented with and without ICH were analyzed using the log rank test. Cumulative and annualized ICH estimates at specific time points were derived from the Kaplan–Meier survival tables. We also performed a restricted survival analysis involving only those cases ascertained at the time of diagnosis at KPNC and compared these results with those obtained from the entire cohort.

We analyzed change in functional status using Rankin score before and after hospital admission for BAVM during initial presentation, as well as before and after admission for subsequent ICH. Rankin score was not part of the original medical record, but was estimated by the chart reviewer from the medical record for the hospital admission. Use of Rankin score from chart abstraction has been previously described.11 We dichotomized Rankin score to >2 (poor outcome) and ≤2 (good outcome), and we used paired McNemar χ² tests.

Results

We identified 793 patients at KPNC with BAVM diagnosed between 1961 and 2001; 3 patients without information regarding initial presentation were excluded from further analysis. Among all BAVM patients identified, 367 (47%) presented with an ICH. Using a hierarchical system,11 the remaining presentations were 190 (24%) with seizure, 114 (14%) with headache, and 119 (15%) with other symptoms, including incidental ones not definitively attributable to the BAVM.

The distribution of patient and BAVM characteristics risks and their respective univariate associations with subsequent ICH under the Cox proportional hazards model are presented in Table 1. Patients who initially presented with ICH had a higher rate of ICH before first treatment (hazard ratio, 2.5; 95% CI, 1.5 to 4.0; P<0.001). This result persisted even after adjusting for age at diagnosis, race–ethnicity, gender, BAVM size, and venous drainage (hazard ratio, 3.6; 95% CI, 1.1 to 11.9; P=0.032).

Including year of diagnosis and use of catheter angiography into the model separately did not alter the estimate. In the final multivariate model, only presentation with ICH demonstrated an independent relationship with subsequent ICH (Table 2). Increased age at diagnosis was marginally significant (P=0.056). An alternative multivariate model excluding
TABLE 2. Multivariate Cox Proportional Hazard Estimates

<table>
<thead>
<tr>
<th>Variables in the Model (N=176)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (per decade)</td>
<td>1.4</td>
<td>1.0–1.9</td>
<td>0.056</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.3</td>
<td>0.4–3.8</td>
<td>0.69</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>1.9</td>
<td>0.6–6.3</td>
<td>0.28</td>
</tr>
<tr>
<td>ICH at presentation</td>
<td>3.6</td>
<td>1.1–11.9</td>
<td>0.032</td>
</tr>
<tr>
<td>BAVM size (&lt;3 cm)</td>
<td>0.7</td>
<td>0.2–2.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Exclusively deep drainage</td>
<td>1.0</td>
<td>0.2–5.5</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

BAVM size resulted in attenuation of the hazard ratio estimate of ICH presentation to 2.6 (95% CI, 1.4 to 5.1), but an increase in significance (P) from 0.032 to 0.004.

A higher proportion of patients from the ICH group were nonwhite (38% versus 25%, P<0.001), but other demographic characteristics were similar. Stratified analyses found no difference in hazard rate ratios of presentation with ICH across race–ethnicity or gender. Further examination of race–ethnic strata was limited by small sample sizes for other subgroups: black (9.0%), Latino (11.5%), Native American (0.1%), and unknown/unrecorded (7.6%).

Follow-up data were available for 350 (95%) of the 367 patients who presented with ICH and 410 (97%) of the 423 patients who presented without ICH (Table 3). In the group that presented with ICH, 32 (9%) had a second ICH before treatment, with 11 of these occurring by the end of the first year; the median time to hemorrhage was 2.4 years. Among patients who presented without ICH, 33 (8%) had an ICH, 8 of the ICH events occurred by the first year, and the median time to hemorrhage was 3.7 years.

The cumulative ICH rates calculated using the Kaplan–Meier method are presented in Table 3 for specific times after diagnosis and are depicted graphically in Figure 1. Compared with the non-ICH group, patients in the ICH group experienced a higher cumulative rate of subsequent ICH (log rank test, P<0.001) and overall had a shorter time at risk and a shorter duration between diagnosis and subsequent ICH. The annualized rates of ICH differed most during the first 2 years but gradually converged over subsequent years (Figure 2).

To address potential ascertainment bias, we restricted the survival analysis to the 572 patients ascertained at time of diagnosis and followed-up prospectively. Overall, the hazard rate ratio for presentation with ICH in this subset of cases was not different from the total cohort in either univariate or multivariate analyses.

Patients who presented with ICH could be assigned Rankin scores more often (345/367) than those with non-ICH presentation (54/423), because they were more likely to have been admitted to the hospital and have associated neurological status detailed in the medical record. All (100%) of the patients who initially presented with ICH had a Rankin score of ≤2 before admission for the initial ICH (Figure 3). This proportion decreased to 67% at discharge (P<0.001), indicating that 33% of the patients had a new deficit after the ICH. From this group, among those who proceeded to have a second ICH, the proportion with a Rankin score of ≤2 decreased from 97% before admission for the second ICH to 66% at discharge (P<0.05), similar to the proportion of patients with new deficits observed for initial ICH. In the non-ICH presentation group, the proportion of patients with a Rankin score of ≤2 decreased minimally from 94% before admission to 89% at discharge. However, at the time of subsequent ICH, the proportion of patients with a Rankin score of ≤2 decreased from 100% before admission to 56% at discharge, similar in magnitude to the change seen in the ICH presentation group.

**Discussion**

This study demonstrates that ICH at initial presentation is the most important predictor of ICH in the natural course of patients harboring a BAVM. It also confirms and elaborates upon previously reported findings (Figures 1 and 2). Our findings offer the first corroborative results from a large community-based, rather than a pure referral, population. Our findings also reconcile the apparent disagreement between studies suggesting differing effects of incident ICH on subsequent ICH: we found an initial difference in ICH rates that diminishes over time and then shows a longer-term trend for the ICH rates to converge (Figure 2). Our examination of the

### TABLE 3. Cumulative and Annualized ICH Rates in Patients Who Presented With and Without ICH

<table>
<thead>
<tr>
<th></th>
<th>ICH</th>
<th>Non-ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of cases</td>
<td>367</td>
<td>423</td>
</tr>
<tr>
<td>ICH after diagnosis</td>
<td>32 (9%)</td>
<td>33 (8%)</td>
</tr>
<tr>
<td>Total follow-up time</td>
<td>854 y</td>
<td>2302 y</td>
</tr>
<tr>
<td>Median time to event*</td>
<td>2.4 y</td>
<td>3.7 y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICH Rate % (±SE)</th>
<th>Cumulative %</th>
<th>Annualized %</th>
<th>Cumulative %</th>
<th>Annualized %</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 1 mo</td>
<td>2.6 (1)</td>
<td>27 (9)</td>
<td>0.5 (0.4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>At 3 mo</td>
<td>4 (1)</td>
<td>14 (5)</td>
<td>1 (0.5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>5 (2)</td>
<td>10 (3)</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>At 1 y</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>3 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>At 2 y</td>
<td>12 (3)</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>At 5 y</td>
<td>21 (5)</td>
<td>5 (1)</td>
<td>9 (2)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>At 10 y</td>
<td>28 (6)</td>
<td>3 (0.7)</td>
<td>15 (3)</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

*ICH rates and standard errors estimated from Kaplan–Meier survival analysis.

*Median time to event describes time to hemorrhage among those patients with hemorrhage in each respective group.
change in Rankin score offers indirect evidence that subsequent ICH is functionally significant to the patient, and the magnitude of the decrease in functional status is similar to that observed for the initial ICH (Figure 3).

Our results confirm and extend previous retrospective observational studies that estimate general risk of spontaneous bleeding to be in the range of 2% to 6% per year, probably higher in the first year. Taken together, the evidence seems to indicate that surgical intervention, if decided on, would be more appropriate sooner rather than later given the steep shape of the hemorrhage-free survival curve during the initial period, especially for patients presenting with ICH (Figures 1 and 2). However, this decision must be weighed against the risk of surgical treatment itself.

The increase in ICH rate was not modified by race–ethnicity or gender and was not biased by the potentially selective ascertainment among cases diagnosed outside of KPNC and ascertained later along the course of their disease.

We could not examine the impact of race–ethnicity in detail because of relatively small sample sizes of race–ethnic groups other than white.

To demonstrate an independent effect of ICH presentation on subsequent ICH, we excluded 1 or more BAVM characteristics associated with hemorrhage from the full multivariate model but could not arrive at a more parsimonious model. Because only 30% of all cases had information on lesion size, we also considered a model excluding BAVM size to see the effect with a more complete dataset. This alternative model also demonstrated the independent effect of presentation with ICH.

Patient selection for surgical treatment could introduce bias into the observed ICH rates in several ways, including introduction of unmeasured covariates. Addition of 2 critical components of the Spetzler–Martin surgical risk score to our multivariate model did not change the nature of the relationship between presentation and subsequent ICH.

Actual patient images were not available to obtain expert neuroradiological adjudication to confirm lesion size or detailed morphological characteristics. The descriptors we report were abstracted from the medical record and were based on published guidelines. Therefore, they serve primarily to verify the population that we present is comparable to populations previously reported. There are a number of important considerations of specificity, sensitivity, and inter-observer agreement in the evaluation of BAVMs that the current study design cannot accommodate.

Our hazard ratio estimate was lower than that reported by Mast et al (adjusted hazard rate ratio: 13.9). This may simply reflect the different BAVM populations seen at an HMO as compared with a tertiary care center, from which Mast et al derived their cases. Two large studies failed to show an effect of ICH presentation on subsequent ICH. One was geographically and temporally dissimilar from the present setting, and the other included a majority who were undergoing a course of embolization and, therefore, did not address pure natural history.
We used Rankin score as a surrogate for functional status to address the question of whether the consequences of a subsequent ICH were worse than an initial ICH. Our results offer a preliminary evaluation of functional changes in subsequent ICH, suggesting that subsequent ICH in the natural course was associated with a decline in functional status, similar to the decline associated with an initial ICH.

The data for Rankin scoring may be influenced by the time elapsed between the ICH and the outcome evaluation; there is often considerable improvement over time after BAVM hemorrhage. Our data represent the functional outcome at hospital discharge for the ICH event. Therefore, our data reflect a short-term outcome, which may overestimate the eventual long-term loss of function.

Some cases may have been missed in our ascertainment, eg, as a result of fatal first ICH or ICD-9 miscoding. However, for this analysis, it was more important that we did not miss subsequent ICH events, and our ability to track inpatient, outpatient, and extramural visits allowed us to detect all subsequent events in our cohort. There are at least subtle effects of the time period of diagnosis on our results, because evaluation and management have changed considerably over the past several decades. Nonetheless, adjusting our analysis for year of ascertainment did not affect our conclusions.

We are aware of 2 large BAVM cohorts being assembled. Data from these sources will be helpful in validating prediction rules derived from our results, which may be of use in formulating treatment decision algorithms and can assist in planning clinical trials.

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References


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