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### Review

# Unruptured brain arteriovenous malformation risk stratification

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# ABSTRACT

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Received 19 February 2025 Accepted 12 April 2025

Cerebral arteriovenous malformations (AVMs) are an uncommon type of central nervous system vascular anomaly that have the potential to rupture and cause intracranial hemorrhage. AVM hemorrhagic risk assessment has been mainly based on anatomical features derived from imaging; the most recent focus on AVM hemodynamics, vessel wall imaging, and molecular analysis of the inflammatory response, provide new insights into the hemorrhagic risk stratification. The greater data availability provided by innovative imaging techniques and biological analysis of biomarkers and genetic polymorphism further demonstrates the existence of a complex interaction between anatomically altered vasculature, non-physiological hemodynamics, and inflammatory molecular activity. The accurate prediction of cerebral AVM rupture, essential to guide the management decision by comparing the risk of observation to the risk of intervention, has yet to be solved. This review of several studies aims to summarize the current evidence on brain AVM rupture risk stratification.

#### INTRODUCTION

Cerebral arteriovenous malformations (AVMs) are an uncommon type of central nervous system vascular anomaly that have the potential to rupture and cause intracranial hemorrhage. These vascular abnormalities consist of direct connections from arteries to veins through an intervening network of low resistance vessels called the nidus, rather than through normal capillary beds, resulting in disrupted hemodynamics. Even though cerebral AVMs affect 1-2 per 100 000 person years, the annual risk of rupture is estimated to be approximately 1-4% per year, and they represent the most common cause of intracranial hemorrhage in younger people, who are subsequently at risk for long term morbidity and mortality.

Understanding hemorrhagic risk is crucial for determining appropriate treatment, especially after the SAIVM (Scottish Audit of Intracranial Vascular Malformations) prospective cohort and the ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) trial results that challenged the impetus on intervening in unruptured AVMs, given the superior outcome of observation over intervention.<sup>2</sup> Currently, the natural history of hemorrhage for cerebral AVMs is controversial, and predicting factors have not been defined univocally. This review aimed to summarize patient demographics and the AVM angioarchitecture,

hemodynamics, and molecular characteristics asso-ciated with an increased risk of brain hemorrhage. **Patient demographics** Multiple studies have analyzed the association between brain AVM rupture and several demo-graphic factors, but results remain controversial. The most consistent risk factor among the different series is a previous history of hemorrhagic presen-tation, which poses, in most cases, an almost imper-ative indication for urgent treatment to avoid recurrent hemorrhage, especially within the first year after the initial episode.<sup>1–6</sup> The annual risk of re-hemorrhage is estimated to be 2–5 times higher re-hemorrhage is estimated to be 2-5 times higher than unruptured AVMs,<sup>17</sup> but risk normalizes after the first year.<sup>3</sup> Sattari *et al*<sup>8</sup> analyzed a cohort of 84 ruptured AVMs and observed a higher risk of second hemorrhage in deep located AVMs compared with cortical ones (8.37% vs 2.68% annual risk), highlighting more complexity in the annual risk prediction after the first hemorrhage.

Few case series reported an increased risk of hemorrhage in older populations<sup>2</sup><sup>9</sup>: older patients are most likely to show AVMs with anatomic risky features, such as aneurysms<sup>9</sup> or venous stenosis,<sup>10</sup> and their lesions have likely been enduring pathologic hemodynamics for a longer time. The increased cumulative year risk of rupture over a lifetime, however, must be weighed against the patient's life expectancy and the risks of treatment for the specific AVM. The crude estimates of lifetime risk of hemorrhage for unruptured AVMs. considering the multiplicative law of probability with a constant year risk of 2-4%, can be approximated to the simplified formula: 105-patient age (%).<sup>1</sup> This can be helpful information for the clinician in the setting of patient counseling about treatment versus observation.

No gender prevalence has been univocally proved to affect the risk of AVM rupture.<sup>2 5</sup> Pregnancy had variable results: a few studies reported an increased risk of up to threefold during pregnancy and the propagation <sup>6</sup> while other page nancy and the puerperium,<sup>6</sup> while other case series failed to find any association.<sup>7</sup> Gajjar et al<sup>11</sup> recently observed an association between stimulant recreational drug use and AVM rupture, and even though Pohjola et al observed considerably higher cigarette smoking rates among AVM patients compared with the general population, the association between tobacco use and ruptured AVMs has not been proved.<sup>12</sup> Overall, patient demographics, apart from a previous history of AVM rupture, have a marginal role in AVM risk stratification and management.

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To cite: Brunozzi D. Alarai A. J NeuroIntervent Surg Epub ahead of print: [please include Day Month Year]. doi:10.1136/jnis-2024-022779



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### **AVM angioarchitecture**

Risk stratification of AVM rupture has been mainly based on the presence of certain radiologic parameters and AVM angioarchitecture features. The location of the AVM has been demonstrated to influence the risk of hemorrhagic presentation: different studies reported an increased risk of bleeding for AVMs with deep, periventricular, or infratentorial locations.<sup>14578</sup> In these locations, AVMs are subjected to increased resistance to blood outflow due to the smaller venous system that the nidus drains into, but are also fed by small perforator feeders that are less resistant to high blood flow.<sup>5</sup> The high blood flow in small perforator feeders can account for the increased incidence of associated aneurysms in infratentorial compared with supratentorial AVMs, a well known independent high risk feature predisposing to hemorrhage.<sup>13 14</sup> Several case series have reported a higher overall hemorrhagic rate in AVMs with associated feeder artery or intranidal aneurysms<sup>2 47</sup> (figure 1A), with an estimated rupture rate up to 7% per year.<sup>7</sup>

Nidus size, instead, has shown controversial results: even though a smaller nidus has been more often associated with an increased risk of rupture,<sup>12</sup> few series demonstrated the opposite, disputing previous reports.<sup>5</sup> Small AVMs are more likely to present with hemorrhage, probably because they are less likely than large ones to become symptomatic without bleeding;



**Figure 1** Brain arteriovenous malformations (AVMs) with angioarchitecture features at increased risk for hemorrhage: (A) Evidence of bilobated aneurysm feeder (white arrow) and intranidal aneurysm (yellow arrow). (B) AVM with single draining vein (arrow). (C) Evidence of draining vein stenosis close to the junction to the superior sagittal sinus (arrow). (D) Evidence of venous ectasia (arrow).

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large AVMs tend to manifest earlier with seizure, mass effect, or stealing phenomenon, overshadowing the hemorrhagic presentation.

When analyzing the AVM venous angioarchitecture, strong rupture predictors have been identified in the presence of deep venous drainage<sup>1 2 4</sup> or single draining vein<sup>1 4</sup> (figure 1B). These venous patterns imply higher resistance to AVM blood flow, with increased upstream pressure gradient within the nidus, justifying the association with hemorrhagic presentation. Similarly, the presence of draining vein stenosis<sup>7</sup> (figure 1C), venous ectasia<sup>27</sup> (figure 1D), and venous tortuosity<sup>15</sup> have been associated with increased hemorrhage in several studies, even though the consensus is not unanimous.<sup>1</sup>

### **AVM hemodynamics**

The angioarchitecture features associated with hemorrhagic risk primarily represent the surrogate of pathologic hemodynamics within the AVM, such as elevated blood inflow or increased outflow obstruction. These features are the epiphenomenon of the vessel adjustment to local turbulence or flow overload more than to increased total AVM flow, and rupture occurs when compensatory mechanisms become inefficient. Indeed, absolute high flow through the AVM is not predictive of hemorrhagic presentation: measurements of total AVM flow on quantitative MR angiography appeared to be unrelated to brain AVM rupture.<sup>16</sup>

It was first observed in the 1990s that AVM rupture was related to elevated arterial feeder pressure and venous outflow restriction, causing increased transmural pressure gradient in the nidus.<sup>17</sup> The pressure measurements performed intraoperatively with superselective angiography<sup>17</sup> were most recently replicated by Zhang *et al*<sup>18</sup> and correlated with increased intranidal flow stasis on DSA, providing a non-invasive radiologic parameter to better stratify the hemorrhagic risk. Furthermore, the presence of aneurysms in AVM feeders is related to increased local wall shear stress (WSS): it has been observed that feeders with aneurysms have similar flow rates but smaller diameters than feeders without aneurysms.<sup>19</sup> Additionally, infratentorial AVMs, fed by smaller arterial feeders, have almost double the prevalence of feeder aneurysms (20.8-47%) compared with supratentorial AVMs (10–20%).<sup>13</sup> This further corroborates the idea that WSS is the likely culprit in AVM feeder aneurysm formation.

The nidus of AVMs seems to have an important role in the hemodynamic interplay, which might contribute to rupture. Shakur *et al*<sup>20</sup> proved that a greater effective cross sectional area of the vessels within the nidus permits higher total AVM flow by lowering resistance within the nidus, ultimately suggesting decreased pressure and risk of rupture, in accordance with previous observations that smaller AVM size carries an increased risk of rupture.<sup>1 2</sup> Guo et al<sup>21</sup> observed an increased risk of rupture in AVMs with shorter time to peak on CT perfusion within the nidus: an increased blood flow with rapid influx and efflux within the AVM nidus is associated with hemorrhagic presentation.

The advent of computational fluid dynamics (CFD) has brought a breakthrough in the understanding of blood flow patterns in cerebrovascular disease, but the complex geometry of AVM compartments does not allow reliable calculation with current imaging methods.<sup>22</sup> Current application of CFD is limited to the hemodynamic analysis of feeding arteries and draining veins to indirectly explore the biological behavior of AVMs. Ma et  $al^{23}$  with CT angiography based CFD models demonstrated that the draining veins of ruptured AVMs had significantly higher

intravascular pressure, linear increase in WSS, and more high velocity segments.

Overall, advanced imaging techniques with quantitative MR, DSA, and CFD allow for better segmentation of feeding arteries, nidus, and draining veins, and deduction of hemodynamic parameters, such as flow and pressure in the individual AVM compartments, which represent valuable complementary information to the angioarchitecture characteristics for risk stratification. All of the studies mentioned above substantiate the new concept that cerebral AVMs are not static lesions but instead evolving vascular entities that endure pathological flow within pathologic vessels during a patient's lifetime. The risky anatomic features may represent an attempt to adapt to the hemodynamic stressor, and rupture may represent the inefficiency or exhaustion of angioarchitecture adjustment.

#### Score prediction

The ongoing research for accurate prediction of AVM rupture and further data availability demonstrate the existence of an intricate hemodynamic interplay between anatomic altered vasculature and non-physiological blood flow. The complexity of molecular, anatomic, and hemodynamic interactions makes the definition of a universal predictive hemorrhagic scoring system arduous: the risk is not just the simple summation of the risk of each separated lesion, but any angioarchitecture risk feature represents a marker of a more severe intracranial vasculopathy.

Several retrospective and prospective studies tried to develop prognostic models by examining the known risky anatomic characteristics based on large patient cohorts and combining them. The R2eD score system, for example, included binary variables (non-white race, small nidus, single arterial feeder, exclusive deep venous drainage, and deep location) and showed an area under the receiver operating characteristic curve of 0.711. The VALE scoring system included four variables (involvement of the cerebral ventricles, presence of a venous aneurysm, deep location of the nidus, and presence of exclusively deep venous drainage) with an area under the receiver operating characteristic curve of 0.73 on a multicenter external validation cohort.<sup>24</sup> More recently, multimodal data analysis and integration have been performed through machine learning algorithms to create a learning weighted model with enhanced accuracy. Zhu *et al* analyzed 28 multidimensional features, including demographic, hemodynamic, and morphological characteristics. They identified an ensemble model that effectively integrates the strengths of individual statistical models, increasing accuracy with an area under the curve of 0.864 on an independent validation dataset.<sup>25</sup> However, none of these scoring systems have been validated on large prospective cohorts. They were developed retrospectively, mainly relying on analyzing the hemorrhagic presentation and not necessarily reflecting the risk of a priori rupture.

#### Molecular signature

Recently, studies on the natural history of brain AVMs have been focusing on rupture promoting factors on a cellular and molecular level, ascribing to increased inflammation and changes in endothelium the cause of instability of vessel wall and, ultimately, rupture.<sup>26 27</sup> Evidence of vessel wall focal inflammation has been demonstrated at a macroscopic level with advanced MR based imaging techniques and has been associated with increased WSS and risk of hemorrhagic presentation.<sup>28 29</sup>

Genetic profiles, protein expression status, and cellular signaling pathways involved in the inflammation mediated vascular wall remodeling and endothelial dysfunction induced by pathologic hemodynamics have been identified. Interleukin

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6 is a proinflammatory cytokine that mediates the acute phase of the inflammatory response, stimulating endothelial activation and smooth muscle cell proliferation by the release of metalloproteinase 9 and vascular endothelial growth factor alpha. These two factors cause the breakdown of the extracellular matrix and vascular remodeling of the AVM nidus, leading to susceptibility to hemorrhage.<sup>26</sup>

Other studies demonstrated that blood vessels of brain AVMs are prone to rupture because of insufficient expression of the platelet derived growth factor subunit B gene and its corresponding receptor, resulting in reduced mural cell recruitment and vascular instability. Reduced pericyte coverage correlates with a more rapid flow through the nidus, which potentiates vascular instability and is associated with more severe microhemorrhages in unruptured human brain AVMs.<sup>27</sup> NOTCH signaling pathways, a cell signaling system present in most animals and humans, are found to be overexpressed in brain AVMs and to be associated with hemorrhagic presentations.<sup>2</sup>

All of the molecular risk factors identified are related to acute inflammation or maturation of the endothelial cell: the increased risk of AVM hemorrhage seems to result from increased cellular inflammation and changes in the endothelium that lead to instability of the vessel wall. It is still unclear how changes in expression of molecular factors are induced and upregulated: flow through the AVM could induce shear stress in certain vessel areas and represent the potential exciting event.<sup>26 28</sup>

Human studies on brain AVM molecular expression are still limited due to the rarity of the disease and the selective indication for AVM resection, in addition to the heterogeneity of the molecular assessment in different studies. Nonetheless, the definition of molecular expression helps in understanding the pathogenesis of AVM rupture and identifying a potential target for prevention and treatment.

Clinical research is rapidly translating preclinical discoveries into therapeutic interventions: a current phase III clinical trial is evaluating the efficacy and safety of bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, in reducing abnormal blood vessel formation in patients with hereditary hemorrhagic telangiectasia harboring brain AVMs.<sup>30</sup> Early phase clinical trials are also in process for nonfamiliar brain AVMs. Trametinib, by inhibiting the MAP/ERK pathway, can prevent the abnormal proliferation of endothelial cells and shows promising results in stabilizing and reducing the progression of existing AVMs. Sotorasib targets AVMs with specific genetic mutations, by selectively inhibiting the mutated pathway.<sup>30</sup> Ongoing research into genetic pathways holds promise for novel therapeutic targets that could transform the management of vascular malformations and reduce the risk of hemorrhagic stroke.

# CONCLUSIONS

Spontaneous brain AVM rupture is an unpredictable event with devastating consequences. Demographic, anatomic, hemodynamic, and molecular factors have been identified to help define the risk of hemorrhagic presentation. The inability to pinpoint a unique etiopathology culprit stems from the complexity of the interaction of the different factors, making a definition of a simplified universal scoring system to stratify that risk difficult.

The accurate prediction of AVM rupture is far from being solved; ongoing research and further data availability demonstrate that the biological behavior of AVMs is continuously evolving during a patient's lifetime. The endoluminal and vessel wall signaling response to shear stress is reflected in vascular instability: from upstream feeders to the nidus and downstream

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