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Unraveling the uncertainty of cerebral aneurysms: challenges in diagnosis, rupture risk prediction, and emerging solutions

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Abstract
Cerebral aneurysms occur when a weakened blood vessel in the brain bulges, potentially leading to life-threatening rupture and bleeding. While most aneurysms are asymptomatic, their sudden rupture poses a significant clinical problem. This review examines the unpredictable nature of cerebral aneurysms and the challenge of diagnosis for this condition. Despite numerous studies on aneurysms, there is uncertainty about why an aneurysm causes bleeding, what increases its chances for rupture, and the probability of rupture in any given timeframe. To examine upcoming treatments and discoveries, this review studies the variability and lack of knowledge in the pathogenesis of cerebral aneurysms, causing a challenging diagnosis, and how recent research has provided insight into learning more about this condition. The review also proposes a scored diagnostic flowchart that can be implemented in a primary care physician's annual visit, so that referral can be obtained for a definitive pre-rupture diagnosis when necessary. Given the uncertainty about the treatment of cerebral aneurysms, more research must be performed in order to accurately predict the time and the probability of rupture, along with potential solutions.

Keywords
Cerebral aneurysms, Pathogenesis, Early detection, Rupture risk, Cerebral aneurysm growth, Diagnostic flowchart, Intracranial, Imaging, Unruptured aneurysms, Artificial Intelligence

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1. Introduction

A cerebral aneurysm is a condition when the wall of a blood vessel in the brain becomes weak and bulges out (1). The bulging aneurysm can put pressure on brain tissues or nerves, which may lead to a leak or rupture. If an aneurysm bursts or ruptures, it may result in life-threatening bleeding into the surrounding tissues, termed a hemorrhage (2), along with other neurological effects and potentially death. Most cerebral aneurysms are small and do not cause problems. However, a ruptured aneurysm becomes a critical situation that needs immediate medical treatment (3). Saccular aneurysms resemble the shape of a "sac" and bulge out of the blood vessel wall, accounting for 80-90% of all brain aneurysms (4). They grow unpredictably depending on several factors such as size, location, shape; and lack visible warning signs of growth (5), with even small aneurysms carrying the risk of rupture. A study conducted by Revilla-Pacheco et al. reported a global prevalence of incidental aneurysms to be 7% (6). This highlights the importance of early detection for individuals who may be at risk, even those who are asymptomatic. In fact, many people with unruptured aneurysms do not show any symptoms (7). This makes diagnosis more difficult, even leading to misdiagnosis at times, due to the lack of information and symptoms present for cerebral aneurysms.

Cerebral aneurysms have several factors contributing to their uncertain growth and rupture, and this literature review examines those factors along with the probability of predicting the risk and time of rupture. For further advancements to be made, there must be improvements in the diagnosis process and exploration into upcoming treatments to investigate this critical gap. Brain aneurysms can rupture without warning, since the brain does not seem to register the aneurysm's presence until it is too late (8). Therefore, this review investigates how to better our understanding of the pathogenesis of cerebral aneurysms to improve diagnosis, create accurate predictions of rupture, and discover new treatment strategies for this condition.

Investigation into the unpredictable nature of cerebral aneurysms is crucial in impacting patient care outcomes and quality of life. Early detection could provide an improved prognosis of the condition and allow for higher survival rates (8). An unruptured brain aneurysm affects ~ 3% of people worldwide (9), with over 6.8 million people in the United States (10). Furthermore, ~ 500,000 deaths worldwide each year are caused by cerebral aneurysms (11), underscoring the importance of research in this area. The challenges of early detection are due to the small aneurysm size and unusual morphology, making it difficult to detect with imaging techniques (12). This can lead to a life-threatening situation that can have severe complications for patients; hence, this study will provide a general overview of what is – and what needs to be – known, especially in terms of diagnosis and prediction.

This study is based on current data available. There are some constraints with this data because much is still not fully understood about the exact causes and how to prevent a cerebral aneurysm from happening. This lack of underlying pathophysiology sets boundaries; however, there will be a focus on future steps being taken to predict growth and rupture risk

(1). While evidence of newer methods of diagnosis and treatment is still evolving, this paper includes and critically evaluates the most up-to-date information currently available.

2. Background

2.1 Causes and symptoms of cerebral aneurysms

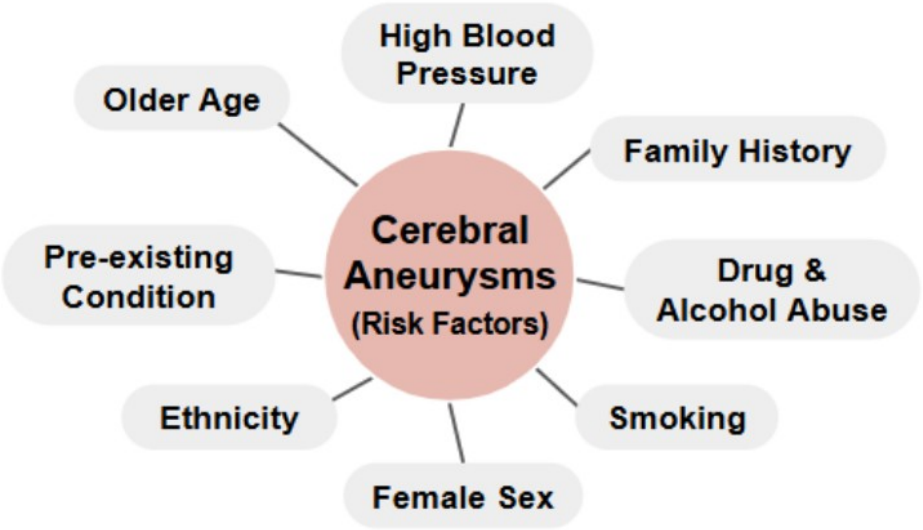

Figure 1. Main risk factors in the formation and rupture of cerebral aneurysms, some risk factors not shown; these additional risk factors are proposed in section 4.2

The cause of cerebral aneurysms is not fully known, but several risk factors have been identified (Figure 1), although; see the subsequent sections – especially section 4.2 - for additional proposed factors. Along with factors of size and structure, when the blood pressure rises in a ballooning shape in a brain blood vessel, this can cause an aneurysm (13). Risk factors include older age, hypertension, smoking, drug and alcohol abuse, and atherosclerosis (14). There is also a genetic factor, where a family history of aneurysms can increase the incidence (14). Certain genetic conditions and syndromes are associated with the development of aneurysms. This includes Polycystic Kidney Disease (PKD), hypercholesterolemia, and other connective tissue disorders (15). There are also certain syndromes, such as Marfan syndrome and Ehlers-Danlos syndrome, that are signs of elevated risk due to structural abnormalities, which weaken blood vessels (15).

Anyone can develop a cerebral aneurysm, yet it is more prevalent in certain groups. Biological sex is another factor, with women at a higher risk than men (16). Women over 40 are the most common group to be diagnosed with a brain aneurysm (13) and have a higher risk of rupture of ~ 1.5 times more than men (11). Additionally, there is a higher prevalence in certain races: African Americans and Hispanics

are twice as likely to have a brain aneurysm compared to Caucasians (11). Another article by Sanchez et al. claims that certain populations, such as Finland or Japan, have an increased aneurysm rupture risk (17).

Most aneurysms are asymptomatic. If unruptured aneurysms do show symptoms, then it generally means they are large and growing (1). This includes pain above and behind the eye, numbness, paralysis on one side of the face, increased eye pupil size, and vision changes (1). When an aneurysm ruptures, symptoms are very apparent, with people describing it as "the worst headache of my life" (18). Other signs are nausea and vomiting, stiff neck, loss of consciousness, blurred vision, seizures, and even death (18). However, the symptoms of an aneurysm may be similar to other conditions, which is why there exists the potential for misdiagnosis. To prevent misdiagnosis, it is essential to possess a knowledge of the underlying principles and causes of cerebral aneurysms.

2.2 Current diagnostic methods for cerebral aneurysms

Most cerebral aneurysms go unnoticed until they rupture or are accidentally seen during imaging tests that are performed for other reasons. Diagnosis is often initiated when symptoms suggest a possible rupture or through screening for individuals with a family history of brain aneurysms (19). A range of imaging and diagnostic methods, both noninvasive and invasive, are utilized for detection (Table 1).

If a ruptured aneurysm is suspected, a head Computed Tomography (CT) scan is the first test used to detect bleeding in the brain (20). In order to pinpoint a cerebral aneurysm, a Computerized Tomography Angiography (CTA) scan, a type of X-ray, can be used to check brain blood vessels, given that an angiogram provides clearer views (19). However, a CT or CTA scan may miss small unruptured aneurysms and is only performed if the patient exhibits clinical signs (many aneurysms don't have signs before rupture). When screening for aneurysms, Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA) is preferred, since this procedure does not expose patients to X-rays (19). Schwab et al. conducted a 2-year study that showed that MRI/MRA studies are often inaccurate in diagnosis, which signifies the need for alternative diagnostic methods (21). Another newer technology is Noninvasive Optimal Vessel Analysis (NOVA) MRA, which noninvasively measures blood flow and outputs interactive 3D images to allow for precise recognition (22). With methods of MRA and NOVA MRA, there is a risk of false positives (21), i.e., for misdiagnosing the presence of an aneurysm when it is actually not present.

Some more invasive methods include lumbar puncture (spinal tap), where a needle is used to extract cerebrospinal fluid from the spine and check for blood markers, which can signal a rupture (22), and Digital Subtraction Angiography (DSA), – the gold standard – where a contrast dye is injected into blood vessels to produce detailed imaging (23). These methods can visualize the brain's blood vessels to identify aneurysms and evaluate size, location, and morphology (20).

Table 1. Main diagnostic methods for cerebral aneurysms and their limitations

Method	Main Use	Invasiveness	Limitations	Reference
CT/CTA	Initial test to detect bleeding	Noninvasive	May miss small-sized aneurysms and is only performed if there are signs shown	(19,20)
MRI/MRA	Screening for unruptured aneurysms	Noninvasive	Evaluation of small vessels is difficult and often leads to an inaccurate diagnosis (and false positives)	(19,21)
NOVA MRA	Measures blood flow through 3D image analysis	Noninvasive	Limited availability, the need for specialized equipment, and the potential for false positives and artifacts	(21-24)
Lumbar Puncture	Detects bleeding not seen in a CT	Invasive	Only detects bleeding, not the aneurysm itself, and is not a primary diagnostic tool	(22)
Cerebral Angiography (DSA)	Produce highly detailed imaging (gold standard)	Invasive	Despite having the most accuracy, the method being invasive has possible complications	(23)

2.3 The growth of cerebral aneurysms

Cerebral aneurysms grow very erratically in shape and size, often without showing any symptoms. Studies report annual growth rates to be between 1.5% to 22%, depending on the individual and different risk factors (25). The weakening of a blood vessel and an inflammatory response can lead to the formation of aneurysms. The main shapes and types of aneurysms are saccular, fusiform, and dissecting (4). Most aneurysms are lesions within the anterior circulation (particularly along the Circle of Willis) in the brain, commonly occurring at bifurcating arteries (25). Whereas aneurysms in the posterior circulation are less common, they are more likely to rupture with negative outcomes, including cognitive impairment and sudden death (25). Growth usually happens in diffuse (parallel wall of aneurysm wall bulging) or focal (bulging of one part of an aneurysm) patterns (26), and sometimes aneurysms can form in new locations previously shown as normal, called *de novo* (27). The difference in shape, size, location, and other factors all affect rupture risk, which is often hard to quantify through imaging.

Small-sized aneurysms, especially those located in anatomically complex areas, are more often missed in imaging. Specifically, the sensitivity drops for aneurysms that are less than 3 mm in size (28), making detection a challenge. Joo et al. found that aneurysms smaller than 7 mm were likely to remain stable for years without rupture (29), but they could still rupture unpredictably, making rupture risk prediction inconsistent. This diagnostic uncertainty stems from not being able to accurately predict cerebral aneurysm growth,

which is why more research is needed to improve rupture risk prediction models.

2.4 Misdiagnosis, lack of biomarkers, and unpredictability

Misdiagnosis of brain aneurysms occurs in up to 25% of patients who initially seek medical attention – most are discharged without a scan (19). These aneurysms often present with no symptoms, and rupture risk is very variable, contributing to their uncertainty (14). In fact, Faluk et al. found that 85% to 90% of unruptured cerebral aneurysms were asymptomatic (30). Aneurysms are found accidentally or wrongly diagnosed, due to misinterpretation of imaging results or the lack of symptoms. Additionally, even individuals with symptomatic cerebral aneurysms were commonly misdiagnosed, as an aneurysm is not always considered in initial evaluation (31). Misdiagnosed patients more often deteriorate or experience rebleeding before a correct diagnosis and definitive management, compared to those who receive correct diagnoses from the outset (31).

Despite promising advancements in imaging techniques and blood tests, currently, no established biomarker can reliably predict aneurysm formation or rupture risk with high accuracy (32). Ruptures can occur suddenly and without any warning, making it a priority to seek earlier detection in order to prevent complications. ~ 50% of patients with ruptured aneurysms exhibit no warning signs before rupture (33), and even if symptoms are apparent, they are often mistakenly associated with other causes. Unawareness of its presence makes early diagnosis extremely difficult. Brain aneurysms are significantly unpredictable to diagnose because of their silent nature, variable growth and rupture risk, and limitations on diagnostic techniques. More research needs to be performed to find better, more predictive diagnostic methods.

3. Methods

A literature review was conducted using the key phrase ‘cerebral aneurysms’, and more specifically, words such as ‘causes’, ‘diagnosis’, ‘treatment’, ‘rupture risk’, ‘pathogenesis’, and ‘new research’, utilizing peer-reviewed articles and scholarly sources from Google Scholar, EBSCO, PubMed, Mayo Clinic, NIH, ScienceDirect, AHA journals, etc. Various databases were used to further explore this topic in detail and identify advancements to incorporate in this systematic review. Qualitative data was used to build discussion and analysis on putting more focus on this topic, along with statistical data to emphasize certain details and predictions of rupture. The search was limited to studies published in the English language. Articles about non-cerebral aneurysms (such as aortic) were excluded from this review, due to irrelevance to the research question. Furthermore, ‘cerebral’, ‘intracranial’, and ‘brain’ are used synonymously in the instance of describing aneurysms.

4. Discussion

4.1 Lack of knowledge in the pathogenesis of cerebral aneurysms

Unruptured cerebral aneurysms occur in 3.6% to 6% of the general population (34). The pathogenesis of cerebral aneurysms is not yet well understood. There is growing evidence of inflammation as a leading factor in the

pathogenesis, through hemodynamic stress and mediated degradation of the extracellular matrix (35). Abnormal hemodynamic forces, such as Wall Shear Stress (WSS), lead to endothelial dysfunction and inflammation, which contributes to aneurysm formation and rupture (36). Soldozy et al. found that hemodynamic insults induce vascular remodeling, weakening the vessel wall and increasing rupture risk (36). The release and imbalance of Matrix MetalloProteinases (MMPs) causes extracellular matrix damage and smooth muscle cell apoptosis (37,38). All these evidenced factors progressively weaken the arterial wall (35) and increase tissue tear, resulting in dilatation and aneurysm formation (39). Many studies have investigated the role of hemodynamics in the formation of cerebral aneurysms using computational simulations; however, their work focuses on idealized geometric aneurysms or surgically made aneurysms in animals (39). This highlights a critical gap in connecting hemodynamics to clinical practice and the lack of applied insight in clinical cases. Other investigations have described only the structural features of aneurysm growth, with very limited studies on the early stages of aneurysm formation (40). For example, Baek et al. created a theoretical model that analyzed tissue growth over time and how stress might cause brain aneurysm enlargement (41).

Another major gap in understanding cerebral aneurysm progression is the role of genetic factors. Studies show that the heritability of intracranial aneurysms is ~ 40% (42), indicating that genetic factors should be included in future research. There exists a comprehensive list of studies that associate genetic variations with the development of brain aneurysms, and specifically, some certainty with inherited genetic variations contributing to risk (43). Specific genes have been linked to and identified in aneurysm development, such as CDKN2A/CDKN2B (chromosome 9p21), SOX17 (chromosome 8q11), and EDNRA (chromosome 4q31) (44). However, the current known loci and variants only explain around 5% of the overall genetic risk, which means other genetic factors probably remain undiscovered (45). Genetic mutations can influence the size and structure and cause weakening arterial walls, making individuals more likely to develop a brain aneurysm. These mutations also negatively affect the extracellular matrix (such as collagen), Vascular Smooth Muscle Cells (VSMC), and hemodynamic forces (43).

The specific inflammatory mediators and pathways involved in the cerebral aneurysm pathogenesis are only partially understood (46). Some of the main inflammatory mediators involved are Nuclear Factor-kB (NF-kB), E-twenty-six family transcription factors (Ets), ProstaGlandin E2 (PGE2), and Monocyte Chemoattractant Protein 1 (MCP-1) (46). Mast cells have been shown to infiltrate an aneurysm vessel throughout pathogenesis: one study analyzed mast cell levels at different intervals in a rat aneurysm model and observed that the number of mast cells in an aneurysm wall significantly increased during its formation (47). Additionally, leukocytes, specifically macrophages and T cells, have been shown to be associated with aneurysm growth (48). Kanematsu et al. found that cerebral aneurysm incidence was lessened in mice with lower macrophage levels and inhibited MCP-1 levels,

when compared to wild-type mice (49). Lastly, inflammatory mediators chemokines (such as MCP-1) and cytokines – particularly Interleukin-1β (IL-1β) and Tumor Necrosis Factor-alpha (TNF-α) as the most studied – are increased to high levels during aneurysm growth, which actively attract inflammatory cells to the aneurysm wall (50). Specific inflammatory mediators can be utilized to create new treatments focused on targeting these inflammatory pathways (46).

The underlying mechanisms of cerebral aneurysm growth are still poorly understood, as growth patterns appear to be more complex than originally thought (35). Researchers need to correlate variables from prediction models to clinical observations to further understand the mechanisms of aneurysm evolution and rupture and gene-environment interactions (39).

4.2 Correlation of risk factors with the probability of rupture for approaching diagnosis

The use of assessing risk factors for estimating rupture of a pre-rupture cerebral aneurysm can be beneficial for approaching diagnosis. Specific risk factors have been correlated with increased probability of rupture. Among them are vitamin D levels, inflammation markers, hypertension, sex, age, family history, along with the appearance of classic symptoms. The key challenge is that individuals do not specifically get tested for cerebral aneurysms. Therefore, clinical diagnosis should preferably be performed during annual visits to a primary care physician, based on results from the annual physical and blood exam. If the exam results show an elevated score for a cerebral aneurysm, then more testing can be conducted to work toward a diagnosis.

Factors such as vitamin D levels and inflammation markers can be routinely tested in annual exams. Studies have shown that lower vitamin D levels are strongly associated with intracranial aneurysm rupture in patients with SubArachnoid Hemorrhage (SAH) (51), as well as in murine models (52). This highlights the value of vitamin D supplementation as a possible alternative to improve the condition of those at risk of a brain aneurysm (52,53). A potential inflammatory biomarker for screening unruptured aneurysms is Orosomucoid 1 (ORM1) (54). Sharma et al. validated that overexpression of ORM1 signified a contribution to aneurysm formation (54). Furthermore, ORM1 is a vitamin D response gene (55), which means that vitamin D could control the progression risk of a cerebral aneurysm by regulating ORM1. Another relevant inflammatory marker is C-Reactive Protein (CRP), with evidence suggesting an increased rupture risk (56) arising from elevated levels. Ongoing research focuses on determining whether markers such as CRP can be integrated into rupture risk prediction models.

Therefore, it is proposed that decreased levels of vitamin D, increased expression of ORM1 and other inflammatory markers such as CRP, comorbiditiy of hypertension, being female, and of older age, along with symptoms and family history disclosed by the patient, should then qualify a patient for further testing to rule out pre-rupture cerebral aneurysms as the diagnosis. This is specially propitious, especially if the patient is referred for

diagnostic scanning anyway – for conditions unrelated to aneurysm. A diagnostic flowchart can be presented in a physician's office during an annual routine exam (Figure 2). Note that the bar for assigning a risk for aneurysms is fairly high (> 6 points), partly because of the non-specificity of symptoms and partly due to the inherently low incidence of the disease. A more nuanced algorithm can obviously be derived, however, the proposed diagnostic chart serves to fill a much-needed gap in predicting pre-rupture aneurysms with abundant caution and minimum resources.

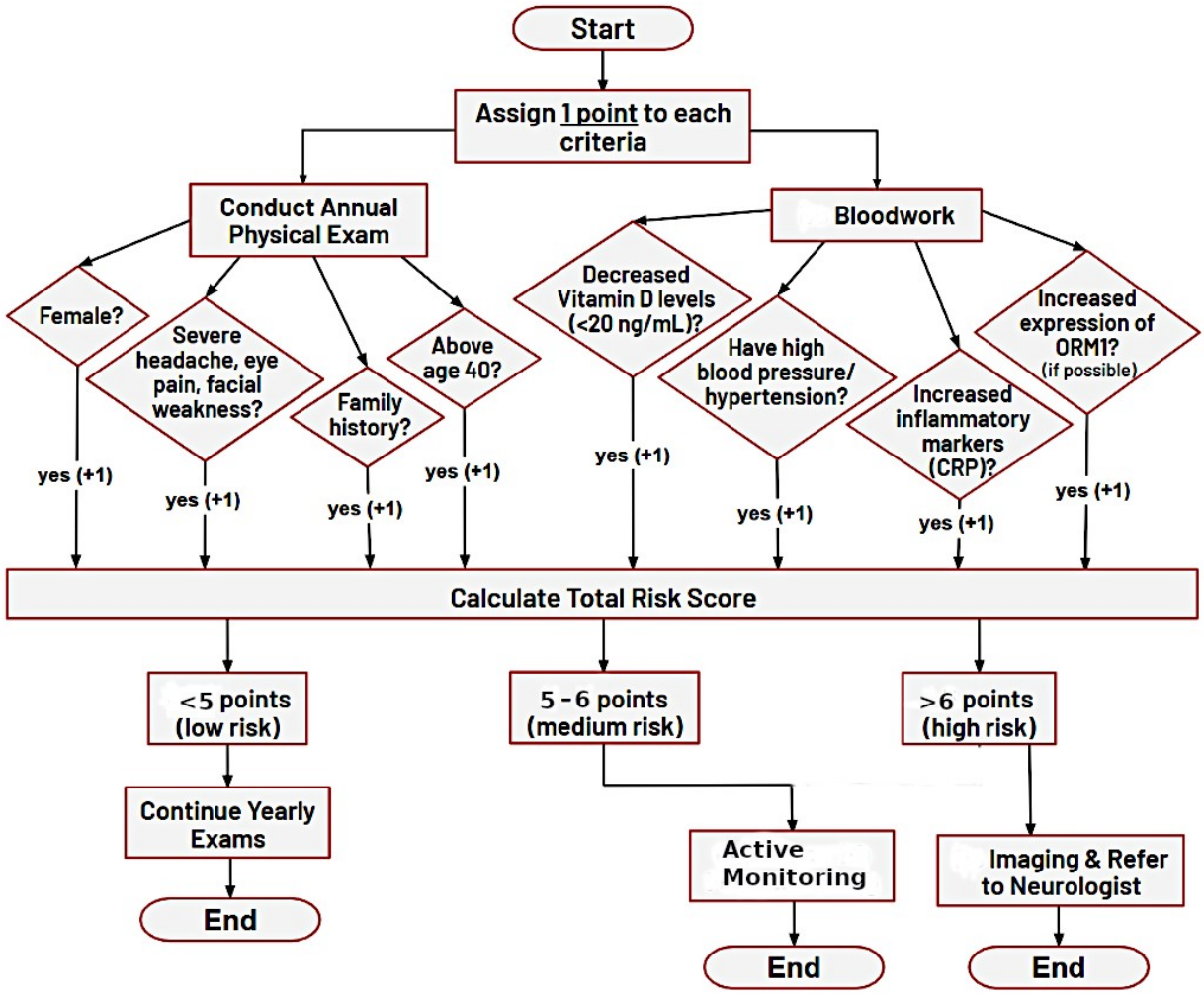

Figure 2. Diagnostic flowchart for pre-rupture cerebral aneurysms

4.3 Advances in cerebral aneurysm diagnosis

Current diagnostic methods for cerebral aneurysms are CT/CTA, MRI/MRA, NOVA MRA, Lumbar Puncture, and DSA. With CTA and MRA being typically used, aneurysms less than 5 mm are difficult to detect in the original images, hence 2D and 3D postprocessing are recommended (57). However, it is important to

note that even the most advanced 3D imaging methods are not infallible, as details may be missed or misinterpreted if examination does not begin with the original images (57).

However, the main limitations with current tools include lower sensitivity in detection and the challenge of accurately visualizing tiny details, like small bulges and the angioarchitecture – the overall aneurysm structure (58). Despite imaging advancements, there are still challenges that need to be addressed to improve diagnosis.

More advanced MRI techniques are being developed to improve detection, including Vessel Wall Imaging (VWI), 4D flow MRI, and Quantitative Susceptibility Mapping (QSM) (59). High-Resolution MRI (HR-MRI) (60) is being developed to enhance the contrast in imaging. The main goal is multimodal imaging, through the combination of various diagnostic imaging tools for better evaluation and detection (60).

The introduction of Artificial Intelligence (AI), lessens the diagnostic burden on radiologists (61). AI Computer-Aided Diagnosis (CAD) systems can assist in aneurysm detection through the use of deep learning algorithms (61). AI CAD demonstrates potential in improving the accuracy of diagnosis and making the workflow more efficient by assisting radiologists (61). For example, deep learning methods like Convolutional Neural Networks (CNNs) can obtain significantly improved results from image analysis (62). AI can also assess risk and predict aneurysm growth to allow more personalized management, using imaging and clinical data (63). However, more validity and algorithm explainabily is needed before AI systems can be integrated as 'stand-alone' modules into clinical settings.

4.4 Rupture risk prediction for cerebral aneurysms

Accurate prediction of rupture risk in cerebral aneurysms is crucial in guiding treatment and preventing complications. Morphological factors play a role in risk prediction: large size (> 7 mm), irregular shape, common locations of the Anterior Communicating Artery (ACoA) and Posterior Communicating Artery (PCoA), and erratic growth (64,65). Additionally, there are risk predictive clinical and computational methods to improve accuracy and validity (Figure 3).

Results from the International Study of Unruptured Intracranial Aneurysms (ISUIA) found a 0.05% annual rate of rupture risk in intracranial aneurysms larger than 10 mm, which increased to 0.5% among patients with a familial history of ruptured aneurysms (66). This trend highlights that an increased aneurysm diameter/size indicates an increased risk of rupture. However, the ISUIA also mentions that the risks of surgery outweigh the annual risk of rupture for aneurysms less than 10 mm in diameter (67). Statistical data have slightly changed since the release of this study; however, this evidence laid the groundwork for researching risk assessment in the following years. Overall, the average risk of rupture now is estimated to be around 0.3% and >15% per 5 years (68).

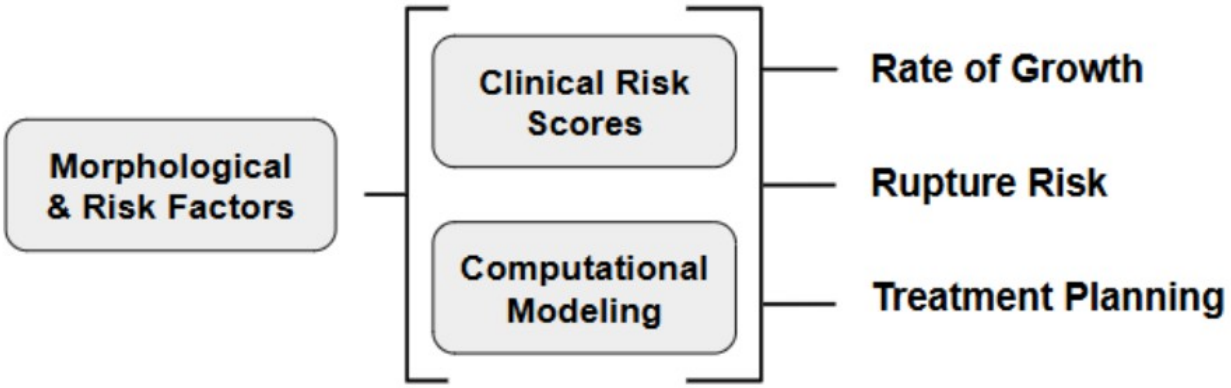

Figure 3. Components of rupture risk prediction to improve accuracy

Table 2. Main clinical risk score prediction models for cerebral aneurysms and limitations

Clinical Risk Scores	Purpose	Limitations	Reference
PHASES	Evaluates a 5-year rupture risk of cerebral aneurysms	Not able to include certain factors, lower validation, and limited predictive power	(17)
ELAPSS	Predicts rupture risk of unruptured cerebral aneurysm growth	Few predictors are excluded due to limited predictive value	(72)
UIATS	Generates a score used to guide treatment decisions	Questioning applicability and failure to accurately provide recommendations	(17)
ISUIA	Estimates unruptured aneurysm risk, with focus on size and location	Selection bias and low sensitivity for detecting aneurysms with rupture risk	(74)
Triple-S	Estimates rupture risk after growth, considers size, shape, and site	Presented risks are an underestimation of rupture risk and not widely known	(64)

Several clinical risk score prediction models have been made available to better estimate cerebral aneurysm rupture risk (Table 2). Since small brain aneurysms can also rupture, these risk prediction algorithms are useful. The Population, Hypertension, Age, Size, Earlier subarachnoid hemorrhage, and Site (PHASES) score assesses patients and aneurysm characteristics to determine a 5-year rupture risk (69,70). PHASES was created from a pooled analysis of 8382 patients with aneurysms (71) and is now the most widely used scoring system. PHASES is not too complex, and variables are part of the clinical history, making them easy to collect (17). Despite its widespread use, PHASES can only evaluate 5-year risk at one specific point in time (17). It is not able to factor in aneurysm

shape and does not include smoking status and biological sex as part of the assessment (17). These limited factors influence the predictive power of PHASES, and the exclusion of some key factors lowers its validity. Another scale is termed the Earlier subarachnoid hemorrhage, aneurysm Location, Age, Population, aneurysm Size and Shape (ELAPSS), which focuses on risk prediction of unruptured intracranial aneurysm growth (72). It scores for 3 and 5-year risks of aneurysm growth (72), with a positive correlation. ELAPSS has similar limitations as PHASES, since a few predictors were excluded due to limited predictive value (72). These are two of many clinical scoring systems utilized to help with predicting rupture risk, as research shifts into integrating various predictive models and incorporating biomarkers and machine learning in models (73).

Computational modeling of cerebral aneurysms is a predictive measure for risk assessment. Derived from 3D clinical angiography, computational modeling helps build a visual representation based on “patient-specific” data (75). The three main approaches of this method are Computational Fluid Dynamics (CFD), Fluid-Structure Interaction (FSI), and Machine Learning (ML), with a focus on analyzing hemodynamics and the likelihood of rupture (76). CFD creates 3D models of fluid flow from a patient CTA scan and uses aneurysm characteristics to calculate wall tension, WSS, Oscillatory Shear Index (OSI), and flow velocity for better estimation (36). However, most CFD studies assume rigid walls, despite cerebral aneurysm walls tending to be very heterogeneous (75). This limitation led to the development of FSI, whose analysis does not assume rigidity in vessel walls and more realistically evaluates wall thickness and mechanical properties (77). Equivalent strain values in the Thin-Walled Area (TWA) were found from FSI analysis, which creates a distinction between unruptured and ruptured aneurysms; however, inaccuracies in patient-specific models and the time and trouble of stimulation are areas of improvement (77). Furthermore, machine learning is a rapid and reliable tool that predicts progression and rupture rate, by building a model based on an existing dataset to make predictions of new cases without human intervention (78). The challenge is that ML needs more clinical validation, due to unclear bias risks and application concerns from existing studies (79). Considering computational modeling is a newer method, there is uncertainty and errors (due to subjectivity) that even the best 3D imaging can not perfectly execute (75). Future research should aim to reduce these discrepancies, thereby facilitating optimal treatment planning.

After detection, the absolute risk of rupture still remains unclear (64). Despite the morphological, clinical, and computational methods utilized for more predictive certainty in cerebral aneurysm rupture risk, it is currently not possible to predict the exact timing of rupture. This is because of the complex nature of aneurysms and poor understanding of the relationship between different risk factors and the risk of rupture (80). The next steps should focus on estimating the time of rupture (in as narrow a timeframe as possible) in order to enhance rupture risk assessment and management.

4.5 Treatment planning and intervention

Models of predicting rupture can be used to guide treatment planning and decisions. Methods such as FSI can create patient-specific strategies and optimize where treatment devices are precisely placed to ensure effective occlusion of blood flow (81). Using various diagnostic imaging models can facilitate the planning of treatment, which makes early intervention necessary (82). Additionally, the use of AI in treatment planning can help identify regions of high rupture risk and aid in selecting specific treatment methods by predicting success rates and complications (76).

The two main treatments for cerebral aneurysms are surgical clipping and endovascular coiling. Surgical clipping involves a small opening that is cut in the skull (via craniotomy) to reach the aneurysm and places a metal clip at its base to seal it off, blocking blood flow and generally preventing rebleeding (83). Endovascular coiling is a procedure where a catheter is inserted into a blood vessel, threading (maneuvering) it to the brain and placing a coil of soft wire into the aneurysm, resulting in a clot that generally provides a seal (similar to clipping) (2). From large dataset studies, specifically among Medicare beneficiaries, trends of annual rates of clipping and coiling in unruptured aneurysms show that a much higher percentage of patients prefer coiling for treatment (80,84). This is because endovascular coiling is a newer and less invasive process that has shorter procedure times and less risk of death (85). However, coiling can lead to a greater risk of rebleeding (84), while clipping has more durability and a smaller chance of rebleeding (86). However, the long-term durability of coiling, while usually effective, is not entirely known yet, and more investigation is needed (86). The treatment type used by each individual depends on a multitude of factors (morphological and age). Li et al. found that aneurysms located in the posterior circulation were associated with coiling, whereas large, wide-necked aneurysms were associated with clipping (84). A more rare option is cerebral bypass, where a bypass is placed to reroute brain blood flow around the aneurysm (87). Medication, such as calcium channel blockers, may also be provided to patients to reduce rupture risk, (88).

For people with unruptured aneurysms, many lifestyle changes are needed, such as regular monitoring of blood pressure and smoking avoidance. Those who have a ruptured aneurysm should focus on rehabilitation through occupational, physical, and speech therapy (89). Developing more effective treatment strategies will be a focus in further research, as risks can recur and have long-term complications. Given that brain aneurysm treatment is a precision medicine approach, looking at risk predictive and hemodynamic factors are anticipated to be important in improving results.

4.6 Perspectives

Despite advances in diagnostic imaging and treatment strategies, the unawareness of pathogenesis, coupled with non-onerous prediction of the presence of a pre-ruptured aneurysm is a significant gap in cerebral aneurysm research.

The molecular mechanisms of intracranial

aneurysms have been overlooked, and specific details are not fully understood, particularly the role of NF-kB as an inflammatory mediator. The NF-kB pathway initiates brain aneurysm development by causing macrophage activation (90). Promising studies have been performed to target this mediator by inhibiting NF-kB and even using it to create treatments. Brangsch et al. suggest that the proinflammatory macrophage accumulation within an aneurysm could be a potential imaging biomarker for rupture risk in the future (32).

Advancements in genetic research have uncovered genetic variants; especially, polymorphism in genes is shown to play a factor in aneurysm formation (76). Understanding epigenetics and the alterations in gene expression with these different variants also holds promise in risk assessment (76). There is still a lack of knowledge of genetic predisposition, and exploring more in that field could help develop unique gene-based therapies (91).

As improvements are made in cerebral aneurysm diagnosis, there are still many obstacles to overcome, indicating the importance of more advanced imaging. Earlier diagnosis would allow for earlier intervention, and that involves utilizing newer (but not more expensive) techniques and AI for optimal outcomes. Currently, a method of automatic simulation of angiographic images from DSA is being developed to enable clinical application (77). Early screening is needed for cerebral aneurysms; this could help lower the unpredictability of this condition and make treatment easier. Burlakoti et al. argue that, given the steady distribution patterns and trends of brain aneurysms for the last 260+ years, early screening for segment variations is highly advised (92). Whereas other scientists, including Vega et al., have a different perspective and do not always recommend screening and immediate intervention after an aneurysm is found. They based their recommendations on various studies; one of which showed that out of 18 patients undergoing surgery, 11 presented with decreased post-surgical neurological function. Furthermore, the increased life expectancy by 2.5 years was hence offset by 19 years of morbidity (34), indicating that the potential harm of surgical treatment may outweigh the slight increase in lifespan. This debate between steady management and surgical intervention is another inconsistency that should be clarified. Although hypothetical; a new blood-based test has been proposed to detect formation and quantify risk (93). Along with predictive biomarkers such as ORM1 and its fortuitous dependence on the ubiquitously investigated Vitamin D in blood tests, these minimally invasive and cost-efficient methods could unlock the holy grail of predicting the presence of unruptured brain aneurysms.

Surgical treatments were always the standard, but recent developments in less-invasive cerebral aneurysm treatment, such as Endovascular coiling, is now paving the way for non-invasive alternatives. Sunitinib, a receptor kinase inhibitor for the platelet-derived growth factor receptor beta (PDGFRB) protein may be a potential non-invasive option for the management of brain aneurysms (94). This treatment has only been experimented on PDGFRB mutated mice, hence the next step would be to confirm these results in humans.

Additionally, nanocarriers for targeted delivery of drugs to the aneurysmal wall are part of ongoing research for treatment, with hopes to be more efficient and personalized (95).

These recommendations all stem from one common objective; to solve the gap between the underlying research of cerebral aneurysms and applying it in a clinical setting. The diagnostic algorithm proposed in this manuscript can improve rupture risk detection, treatment planning, and clinical workflow. Biomarkers, anti-inflammatory and non-invasive therapies, diagnostic and risk-assessing tools incorporating AI, and personalized screening methods can be investigated. This review can serve as a basis for future work, as well as incorporation into current diagnostic protocols, since it outlines all the main areas of focus and components of brain aneurysm research.

5. Conclusion

The often-silent progression and devastating consequences of rupture in cerebral aneurysms makes it a serious health issue that requires further research. Despite an extensive body of literature on the subject, significant gaps still remain in the underlying mechanisms of aneurysm formation, growth, and rupture. The unpredictability of cerebral aneurysms makes diagnosis and intervention challenging. This review highlights the urgency of new diagnostic and treatment methods, along with more research to accurately predict the risk of rupture and identify reliable biomarkers and genetic factors. A preliminary quantitative diagnostic algorithm is proposed, using easily obtainable data from annual physical exams and blood testing; routinely performed in a primary care physician environment; whose score can alert the physician and patient to the possibility of the presence of a pre-rupture aneurysm. Depending on the algorithm score, active monitoring may be initiated with more frequent visits and lifestyle changes; or the patient could be referred for specialized scans. The use of new technologies, including artificial intelligence and machine learning, holds promise for offering advancements in the management of cerebral aneurysms. Advancing knowledge in these areas will be crucial in improving outcomes, guiding clinical workflow, and transitioning towards personalized medicine.

6. References

1. National Institute of Neurological Disorders and Stroke. (2023). Cerebral Aneurysms. https://www.ninds.nih.gov/health-information/disorders/cerebral-aneurysms

2. Cleveland Clinic. (2019). Brain aneurysm: Symptoms & information. https://my.clevelandclinic.org/health/diseases/16800-brain-aneurysm

3. Mayo Clinic. (2023). Brain aneurysm - Symptoms and causes. https://www.mayoclinic.org/diseases-conditions/brain-aneurysm/symptoms-causes/syc-20361483

4. UT Health San Antonio Long School of Medicine. (n.d.). Brain Aneurysm Treatment. Neurosurgery. https://lsom.uthscsa.edu/neurosurgery/clinical-practice/brain-aneurysms/

5. Keedy, A. (2006). An overview of intracranial aneurysms. McGill Journal of Medicine : MJM, 9(2), 141. https://pmc.ncbi.nlm.nih.gov/articles/PMC2323531/

6. Revilla-Pacheco, F., Escalante-Seyffert, M. C., Herrada-Pineda, T., Manrique-Guzmán, S., Pérez-Zúñiga, I., Rangel-Suarez, S., et al. (2018). Prevalence of Incidental Clinoid Segment Saccular Aneurysms. World Neurosurgery, 115, e244–e251. https://doi.org/10.1016/j.wneu.2018.04.027

7. deBlecourt, M. (2024). Unruptured Brain Aneurysm: Know the Symptoms and When to Seek Care. Duke Health. https://www.dukehealth.org/blog/unruptured-brain-aneurysm-symptoms-when-seek-care

8. The University of Kansas Health System. (2022). Most Brain Aneurysms Don't Cause Symptoms. https://www.kansashealthsystem.com/news-room/blog/2022/05/most-aneurysms-dont-have-symptoms

9. Hackenberg, K. A. M., Hänggi, D., Etminan, N. (2018). Unruptured Intracranial Aneurysms. Stroke, 49(9), 2268–2275. https://doi.org/10.1161/strokeaha.118.021030

10. West, M., Han, S. (2023). Brain aneurysms: Prevalence and more. MedicalNewsToday. https://www.medicalnewstoday.com/articles/how-common-are-brain-aneurysms

11. Brain Aneurysm Foundation. (n.d.). Statistics and Facts. https://www.bafound.org/statistics-and-facts/

12. Timmins, K. M., van der Schaaf, I. C., Bennink, E., Ruigrok, Y. M., An, X., Baumgartner, M., et al. (2021). Comparing methods of detecting and segmenting unruptured intracranial aneurysms on TOF-MRAS: The ADAM challenge. NeuroImage, 238(1053-8119), 118216. https://doi.org/10.1016/j.neuroimage.2021.118216

13. Brigham and Women's Hospital. (n.d.). Brain Aneurysm: Symptoms, Causes, Risk Factors. https://www.brighamandwomens.org/neurosurgery/brain-aneurysm

14. Jersey, A. M., Foster, D. M. (2023). Cerebral Aneurysm. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK507902/

15. Rice-Canetto, T. E., Ueno, A., Whitney, E., Reier, L., Houston, R., Siddiqi, J. (2025). A Review of the Current Literature on Cerebral Aneurysms. Cureus, 17(3). e80223. https://doi.org/10.7759/cureus.80223

16. Zuurbier, C. C. M., Molenberg, R., Mensing, L. A., Wermer, M. J. H., Juvela, S., Lindgren, A. E., et al. (2022). Sex Difference and Rupture Rate of Intracranial Aneurysms: An Individual Patient Data Meta-Analysis. Stroke, 53(2), 362–369. https://doi.org/10.1161/strokeaha.121.035187

17. Sanchez, S., Miller, J. M., Samaniego, E. A. (2023). Clinical Scales in Aneurysm Rupture Prediction. Stroke: Vascular and Interventional Neurology, 4(1). https://doi.org/10.1161/svin.123.000625

18. John Hopkins Medicine. (n.d.). Cerebral Aneurysm. https://www.hopkinsmedicine.org/health/conditions-and-diseases/cerebral-aneurysm

19. Brain Aneurysm Foundation. (2024). Diagnosis and Screening. https://www.bafound.org/understanding-brain-aneurysms/warning-signs-symptoms/diagnosis-and-screening/

20. UI Health. (n.d.). Diagnosing a Brain Aneurysm. https://hospital.uillinois.edu/primary-and-specialty-care/neurology-and-neurosurgery/neurological-conditions-we-treat/brain-aneurysm/diagnosis-imaging

21. Schwab, K. E., Gailloud, P., Wyse, G., Tamargo, R. J. (2008). Limitations of magnetic resonance imaging and magnetic resonance angiography in the diagnosis of intracranial aneurysms. Neurosurgery, 63(1), 29–35. https://doi.org/10.1227/01.neu.0000335068.53190.46

22. OHSU Brain Institute. (n.d.). Brain Aneurysm Diagnosis and Treatment. https://www.ohsu.edu/brain-institute/brain-aneurysm-diagnosis-and-treatment

23. Stafa, A., Leonardi, M. (2008). Role of Neuroradiology in Evaluating Cerebral Aneurysms. Interventional Neuroradiology, 14(Suppl 1), 23–37. https://doi.org/10.1177/15910199080140s106

24. Hwang, Z.-A., Li, C.-W., Lin, C.-Y. E., Chen, J.-H., Chen, C.-Y., Chan, W. P. (2021). Intensity of arterial structure acquired by Silent MRA estimates cerebral blood flow. Insights into Imaging, 12(1). https://doi.org/10.1186/s13244-021-01132-0

25. Tawk, R. G., Hasan, T. F., D'Souza, C. E., Peel, J. B., Freeman, W. D. (2021). Diagnosis and Treatment of Unruptured Intracranial Aneurysms and Aneurysmal Subarachnoid Hemorrhage. Mayo Clinic Proceedings, 96(7), 1970–2000. https://doi.org/10.1016/j.mayocp.2021.01.005

26. Lee, J., Kong, M. H., Kim, J. H., Jang, S. Y., Kim, S., Hong, S., Song, K. Y. (2022). Analysis of Factors Related to Growth and Growth Patterns of Unruptured Intracranial Aneurysms. Korean Journal of Neurotrauma, 18(1), 45–55. https://doi.org/10.13004/kjnt.2022.18.e7

27. Obray, R., Clatterbuck, R., Olvi, A., Tamargo, R., Murphy, K. J., Gailloud, P. (2003). De Novo Aneurysm Formation 6 and 22 Months after Initial Presentation in Two Patients. AJNR: American Journal of Neuroradiology, 24(9), 1811. https://pmc.ncbi.nlm.nih.gov/articles/PMC7976314/

28. Thompson, B. G., Brown, R. D., Amin-Hanjani, S., Broderick, J. P., Cockroft, K. M., Connolly, E. S., et al. (2015). Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms. Stroke, 46(8), 2368–2400. https://doi.org/10.1161/str.0000000000000070

29. Joo, S. W., Lee, S.-I., Noh, S. J., Jeong, Y. G., Kim, M. S., Jeong, Y. T. (2009). What Is the Significance of a Large Number of Ruptured Aneurysms Smaller than 7 mm in Diameter? Journal of Korean Neurosurgical Society, 45(2), 85–85. https://doi.org/10.3340/jkns.2009.45.2.85

30. Faluk, M., De Jesus, O. (2024). Saccular Aneurysm. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557867/

31. Mayer, P. L., Awad, I. A., Todor, R., Harbaugh, K., Varnavas, G., Lansen, T. A., et al. (1996). Misdiagnosis of Symptomatic Cerebral Aneurysm. Stroke, 27(9), 1558–1563. https://doi.org/10.1161/01.str.27.9.1558

32. Brangsch, J., Reimann, C., Kaufmann, J. O., Adams, L. C., Onthank, D. C., Thöne-Reineke, C., et al. (2019). Concurrent Molecular Magnetic Resonance Imaging of Inflammatory Activity and Extracellular Matrix Degradation for the Prediction of Aneurysm Rupture. Circulation: Cardiovascular Imaging, 12(3). https://doi.org/10.1161/circimaging.118.008707

33. Okawara, S.-H. (1973). Warning signs prior to rupture of an intracranial aneurysm. Journal of Neurosurgery, 38(5), 575–580. https://doi.org/10.3171/jns.1973.38.5.0575

34. Vega, C., Kwoon, J. V., Lavine, S. D. (2002). Intracranial Aneurysms: Current Evidence and Clinical Practice. American Family Physician, 66(4), 601–609. https://www.aafp.org/pubs/afp/issues/2002/0815/p601.html

35. Chalouhi, N., Hoh, B. L., Hasan, D. (2013). Review of Cerebral Aneurysm Formation, Growth, and Rupture. Stroke, 44(12), 3613–3622. https://doi.org/10.1161/strokeaha.113.002390

36. Soldozy, S., Norat, P., Elsarrag, M., Chatrath, A., Costello, J. S., Sokolowski, J. D., et al. (2019). The biophysical role of hemodynamics in the pathogenesis of cerebral aneurysm formation and rupture. Neurosurgical Focus, 47(1), E11. https://doi.org/10.3171/2019.4.focus19232

37. Jung, K.-H. (2018). New Pathophysiological Considerations on Cerebral Aneurysms. Neurointervention, 13(2), 73–83. https://doi.org/10.5469/neuroint.2018.01011

38. McCormick, M. L., Gavrila, D., Weintraub, N. L. (2007). Role of Oxidative Stress in the Pathogenesis of Abdominal Aortic Aneurysms. Arteriosclerosis, Thrombosis, and Vascular Biology, 27(3), 461–469. https://doi.org/10.1161/01.atv.0000257552.94483.14

39. Sforza, D. M., Putman, C. M., Cebral, J. R. (2009). Hemodynamics of Cerebral Aneurysms. Annual Review of Fluid Mechanics, 41(1), 91–107. https://doi.org/10.1146/annurev.fluid.40.111406.102126

40. Nabaei, M., Fatouraee, N. (2012). Computational modeling of formation of a cerebral aneurysm under the influence of smooth muscle cell relaxation. Journal of Mechanics in Medicine and Biology, 12(01), 1250006. https://doi.org/10.1142/s0219519411004599

41. Baek, S., Rajagopal, K. R., Humphrey, J. D. (2006). A Theoretical Model of Enlarging Intracranial Fusiform Aneurysms. Journal of Biomechanical Engineering, 128(1), 142–149. https://doi.org/10.1115/1.2132374

42. Bakker, M. K., Ruigrok, Y. M. (2021). Genetics of Intracranial Aneurysms. Stroke, 52(9), 3004–3012. https://doi.org/10.1161/strokeaha.120.032621

43. Toader, C., Eva, L., Bratu, B.-G., Covache-Busuioc, R.-A., Costin, H. P., Dumitrascu, D.-I., Glavan, L.-A., Corlatescu, A. D., Ciurea, A. V. (2023). Intracranial Aneurysms and Genetics: An Extensive Overview of Genomic Variations, Underlying Molecular Dynamics, Inflammatory Indicators, and Forward-Looking Insights. Brain Sciences, 13(10), 1454–1454. https://doi.org/10.3390/brainsci13101454

44. Alg, V. S., Sofat, R., Houlden, H., Werring, D. J. (2013). Genetic risk factors for intracranial aneurysms: A meta-analysis in more than 116,000 individuals. Neurology, 80(23), 2154–2165. https://doi.org/10.1212/wnl.0b013e318295d751

45. Mohan, D., Munteanu, V., Coman, T., Ciurea, A. (2015). Genetic factors involves in intracranial aneurysms – actualities. Journal of Medicine and Life, 8(3), 336. http://pmc.ncbi.nlm.nih.gov/articles/PMC4556916/

46. Fennell, V. S., Kalani, M. Y. S., Atwal, G., Martirosyan, N. L., Spetzler, R. F. (2016). Biology of Saccular Cerebral Aneurysms: A Review of Current Understanding and Future Directions. Frontiers in Surgery, 3. https://doi.org/10.3389/fsurg.2016.00043

47. Ishibashi, R., Aoki, T., Nishimura, M., Hashimoto, N., Miyamoto, S. (2010). Contribution of mast cells to cerebral aneurysm formation. Current Neurovascular Research, 7(2), 113–124. https://doi.org/10.2174/156720210791184916

48. Hasan, D., Hudson, J., Dooley, S. (2015). Inflammation in human cerebral aneurysms: pathogenesis, diagnostic imaging, genetics, and therapeutics. Neuroimmunology and Neuroinflammation, 2(2), 77. https://doi.org/10.4103/2347-8659.154433

49. Kanematsu, Y., Kanematsu, M., Kurihara, C., Tada, Y., Tsou, T.-L., van Rooijen, N., et al. (2010). Critical Roles of Macrophages in the Formation of Intracranial Aneurysm. Stroke, 42(1), 173–178. https://doi.org/10.1161/strokeaha.110.590976

50. Chalouhi, N., Points, L., Pierce, G. L., Ballas, Z., Jabbour, P., Hasan, D. (2013). Localized Increase of Chemokines in the Lumen of Human Cerebral Aneurysms. Stroke, 44(9), 2594–2597. https://doi.org/10.1161/strokeaha.113.002361

51. Wei, S., Yuan, X., Li, D., Fan, F., Guo, X., Xu, Y., Guan, S. (2022). Vitamin D level is associated with rupture of intracranial aneurysm in patients with subarachnoid hemorrhage. Frontiers in Neurology, 13. https://doi.org/10.3389/fneur.2022.890950

52. Kimura, T., Rahmani, R., Miyamoto, T., Kamio, Y., Kudo, D., Sato, H., et al. (2024). Vitamin D deficiency promotes intracranial aneurysm rupture. Journal of Cerebral Blood Flow & Metabolism, 44(7), 1174–1183. https://doi.org/10.1177/0271678x241226750

53. Chung, Y. J., Kim, H. S., Jang, S. J. (2020). Risk Factor of Cerebral aneurysm and Correlation with Vitamin D Deficiency. Journal of Korean Society of Geriatric Neurosurgery, 16(1), 7–11. https://doi.org/10.51638/jksgn.20.00052

54. Sharma, T., Datta, K. K., Kumar, M., Dey, G., Khan, A. A., Mangalaparthi, K. K., et al. (2020). Intracranial Aneurysm Biomarker Candidates Identified by a Proteome-Wide Study. OMICS: A Journal of Integrative Biology, 24(8), 483–492. https://doi.org/10.1089/omi.2020.0057

55. Gemelli, C., Martello, A., Montanari, M., Marani, T. Z., Salsi, V., Zappavigna, V., et al. (2013). The Orosomucoid 1 protein is involved in the vitamin D – mediated macrophage de-activation process. Experimental Cell Research, 319(20), 3201–3213. https://doi.org/10.1016/j.yexcr.2013.08.017

56. Al-Kholy, S., Kenawi, M., Battah, A., Al-Desouky, M. (2018). Inflammatory markers and cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Research and Opinion in Anesthesia and Intensive Care, 5(2), 127. https://doi.org/10.4103/roaic.roaic_35_17

57. Konovalov, A., Gadzhiagaev, V., Artemyev, A., Okishev, D., Pilipenko, Y., Grebenev, F., Eliava, S. (2024). A Systematic Review and Case Illustrations of Misdiagnosing Intracranial Aneurysms. Cureus, 16(4). https://doi.org/10.7759/cureus.59185

58. Okahara, M., Kiyosue, H., Yamashita, M., Nagatomi, H., Hata, H., Saginoya, T., Sagara, Y., & Mori, H. (2002). Diagnostic Accuracy of Magnetic Resonance Angiography for Cerebral Aneurysms in Correlation With 3D–Digital Subtraction Angiographic Images. Stroke, 33(7), 1803–1808. https://doi.org/10.1161/01.str.0000019510.32145.a9

59. Leon-Rojas, J. E. (2025). Beyond Size: Advanced MRI Breakthroughs in Predicting Intracranial Aneurysm Rupture Risk. Journal of Clinical Medicine, 14(9), 3158. https://doi.org/10.3390/jcm14093158

60. Maupu, C., Lebas, H., Boulaftali, Y. (2022). Imaging Modalities for Intracranial Aneurysm: More Than Meets the Eye. Frontiers in Cardiovascular Medicine, 9. https://doi.org/10.3389/fcvm.2022.793072

61. Delfan, N., Abbasi, F., Emamzadeh, N., Bahri, A., Parvaresh Rizi, M., Motamedi, A., Moshiri, B., Iranmehr, A. (2025). Advancing Intracranial Aneurysm Detection: A Comprehensive Systematic Review and Meta-analysis of Deep Learning Models Performance, Clinical Integration, and Future Directions. Journal of Clinical Neuroscience, 136, 111243. https://doi.org/10.1016/j.jocn.2025.111243v

62. An, X., He, J., Di, Y., Wang, M., Luo, B., Huang, Y., Ming, D. (2022). Intracranial Aneurysm Rupture Risk Estimation With Multidimensional Feature Fusion. Frontiers in Neuroscience, 16. https://doi.org/10.3389/fnins.2022.813056

63. Tjoumakaris, S. I., Hanel, R., Mocco, J., M. Ali-Aziz Sultan, Froehler, M., Lieber, B. B., et al. (2024). ARISE I Consensus Review on the Management of Intracranial Aneurysms. Stroke, 55(5), 1428–1437. https://doi.org/10.1161/strokeaha.123.046208

64. van der Kamp, L. T., Rinkel, G. J. E., Verbaan, D., van den Berg, R., Vandertop, W. P., Murayama, Y., et al. (2021). Risk of Rupture After Intracranial Aneurysm Growth. JAMA Neurology, 78(10), 1228. https://doi.org/10.1001/jamaneurol.2021.2915

65. Ikawa, F., Morita, A., Tominari, S., Nakayama, T., Shiokawa, Y., Date, I., et al. (2019). Rupture risk of small unruptured cerebral aneurysms. Journal of Neurosurgery, 132(1), 69–78. https://doi.org/10.3171/2018.9.jns181736

66. Silva, M. A., Chen, S., Starke, R. M. (2022). Unruptured cerebral aneurysm risk stratification: Background, current research, and future directions in aneurysm assessment. Surgical Neurology International, 13, 182. https://doi.org/10.25259/sni_1112_2021

67. The International Study of Unruptured Intracranial Aneurysms Investigators. (1998). Unruptured Intracranial Aneurysms — Risk of Rupture and Risks of Surgical Intervention. New England Journal of Medicine, 339(24), 1725–1733. https://doi.org/10.1056/nejm199812103392401

68. Bijlenga, P., Gondar, R., Schilling, S., Morel, S., Hirsch, S., Cuony, J., et al. (2017). PHASES Score for the Management of Intracranial Aneurysm. Stroke, 48(8), 2105–2112. https://doi.org/10.1161/strokeaha.117.017391

69. Koester, S. W., Rhodenhiser, E. G., Dabrowski, S. J., Scherschinski, L., Hartke, J. N., Naik, A., et al. (2023). Optimal PHASES Scoring for Risk Stratification of Surgically Treated Unruptured Aneurysms. World Neurosurgery, 183, e447–e453. https://doi.org/10.1016/j.wneu.2023.12.119

70. Tutino, V. M., Poppenberg, K. E. (2025). dbGaP Study. https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs003072.v1.p1

71. Greving, J. P., Wermer, M. J. H., Brown, R. D., Morita, A., Juvela, S., Yonekura, M., et al. (2014). Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. The Lancet. Neurology, 13(1), 59–66. https://doi.org/10.1016/S1474-4422(13)70263-1

72. van Kammen, M. S., Greving, J. P., Kuroda, S., Kashiwazaki, D., Morita, A., Shiokawa, Y., et al. (2019). External Validation of the ELAPSS Score for Prediction of Unruptured Intracranial Aneurysm Growth Risk. Journal of Stroke, 21(3), 340–346. https://doi.org/10.5853/jos.2019.01277

73. Zakeri, M., Atef, A., Aziznia, M., Jafari, A. (2025). Comprehensive Cerebral Aneurysm Rupture Prediction: From Clustering to Deep Learning. MedRxiv. https://doi.org/10.1101/2024.10.31.24316531

74. Hernández-Durán, S., Mielke, D., Rohde, V., Malinova, V. (2020). Is the unruptured intracranial aneurysm treatment score (UIATS) sensitive enough to detect aneurysms at risk of rupture? Neurosurgical Review, 44(2), 987–993. https://doi.org/10.1007/s10143-020-01246-x

75. Steinman, D. A., Pereira, V. M. (2019). How patient specific are patient-specific computational models of cerebral aneurysms? An overview of sources of error and variability. Neurosurgical Focus, 47(1), E14. https://doi.org/10.3171/2019.4.focus19123

76. Wang, X., Huang, X. (2024). Risk factors and predictive indicators of rupture in cerebral aneurysms. Frontiers in Physiology, 15. https://doi.org/10.3389/fphys.2024.1454016

77. Cho, K.-C., Yang, H., Kim, J.-J., Oh, J. H., Kim, Y. B. (2020). Prediction of rupture risk in cerebral aneurysms by comparing clinical cases with fluid-structure interaction analyses. Scientific Reports, 10(1), 18237. https://doi.org/10.1038/s41598-020-75362-5

78. Nabaei, M. (2022). Cerebral aneurysm evolution modeling from microstructural computational models to machine learning: A review. Computational Biology and Chemistry, 98, 107676. https://doi.org/10.1016/j.compbiolchem.2022.107676

79. Daga, K., Agarwal, S., Moti, Z., Lee, M. B. K., Din, M., Wood, D., Modat, M., Booth, T. C. (2025). Machine Learning Algorithms to Predict the Risk of Rupture of Intracranial Aneurysms: a Systematic Review. Clinical Neuroradiology, 35, 3–16. https://doi.org/10.1007/s00062-024-01474-4

80. Bekelis, K., Goodney, P. R., Dzebisashvili, N., Goodman, D. C., Bronner, K. K. (2014). Cerebral aneurysms: frequency and variation. The Dartmouth Institute for Health Policy and Clinical Practice. https://www.ncbi.nlm.nih.gov/books/NBK586759/

81. Hachem, E., Meliga, P., Goetz, A., Rico, P. J., Viquerat, J., Larcher, A., et al. (2023). Reinforcement learning for patient-specific optimal stenting of intracranial aneurysms. Scientific Reports, 13(1). https://doi.org/10.1038/s41598-023-34007-z

82. Andereggen, L., Gralla, J., Andres, R. H., Weber, S., Schroth, G., Beck, J., et al. (2016). Stereolithographic models in the interdisciplinary planning of treatment for complex intracranial aneurysms. Acta Neurochirurgica, 158(9), 1711–1720. https://doi.org/10.1007/s00701-016-2892-3

83. New York-Presbyterian. (2025). Brain (Cerebral) Aneurysm: Diagnosis & Treatment. https://www.nyp.org/neuro/brain-aneurysm/treatment#treatment

84. Li, H., Pan, R., Wang, H., Rong, X., Yin, Z., Milgrom, D. P., Shi, X., Tang, Y., Peng, Y. (2012). Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. Stroke, 44(1), 29–37. https://doi.org/10.1161/STROKEAHA.112.663559

85. Deshmukh, A. S., Priola, S. M., Katsanos, A. H., Scalia, G., Costa, A., Srivastava, A., Hawkes, C. (2024). The Management of Intracranial Aneurysms: Current Trends and Future Directions. Neurology International, 16(1), 74–94. https://doi.org/10.3390/neurolint16010005

86. Molyneux, A. J., Birks, J., Clarke, A., Sneade, M., Kerr, R. (2015). The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). The Lancet, 385(9969), 691–697. https://doi.org/10.1016/S0140-6736(14)60975-2

87. UI Health. (n.d.). Brain Aneurysm Treatment. Hospital.uillinois.edu. https://hospital.uillinois.edu/primary-and-specialty-care/neurology-and-neurosurgery/neurological-conditions-we-treat/brain-aneurysm/treatment

88. Shimizu, K., Imamura, H., Tani, S., Adachi, H., Sakai, C., Ishii, A., et al. (2021). Candidate drugs for preventive treatment of unruptured intracranial aneurysms: A cross-sectional study. PLOS ONE, 16(2), e0246865. https://doi.org/10.1371/journal.pone.0246865

89. Brain Aneurysm Foundation. (2024). Rehabilitation. https://www.bafound.org/treatment-recovery/rehabilitation/

90. Aoki, T., Kataoka, H., Shimamura, M., Nakagami, H., Wakayama, K., Moriwaki, T., et al. (2007). NF-κB Is a Key Mediator of Cerebral Aneurysm Formation. Circulation, 116(24), 2830–2840. https://doi.org/10.1161/circulationaha.107.728303

91. Theodotou, C. B., Snelling, B. M., Sur, S., Haussen, D. C., Peterson, E. C., Elhammady, M. S. (2017). Genetic associations of intracranial aneurysm formation and sub-arachnoid

hemorrhage. Asian Journal of Neurosurgery, 12(3), 374. https://doi.org/10.4103/1793-5482.180972

92. Burlakoti, A., Kumaratilake, J., Taylor, J., Henneberg, M. (2024). Trend of cerebral aneurysms over the past two centuries: need for early screening. BMJ Open, 14(2), e081290–e081290. https://doi.org/10.1136/bmjopen-2023-081290

93. Nowicki, K. W., Mittal, A. M., Abou-Al-Shaar, H., Rochlin, E. K., Lang, M. J., Gross, B. A., Friedlander, R. M. (2023). A Future Blood Test to Detect Cerebral Aneurysms. Cellular and Molecular Neurobiology, 43(6), 2697–2711. https://doi.org/10.1007/s10571-023-01346-4

94. Floersh, H. (2023). Cancer drug from Pfizer appears to stop aneurysm growth, opening door to nonsurgical treatment. Fierce Biotech. https://www.fiercebiotech.com/research/cancer-drug-stops-aneurysm-growth-opening-door-non-surgical-treatment

95. Toader, C., Radoi, M. P., Covlea, C.-A., Covache-Busuioc, R.-A., Ilie, M. M., Glavan, L.-A., et al. (2024). Cerebral Aneurysm: Filling the Gap Between Pathophysiology and Nanocarriers. International Journal of Molecular Sciences, 25(22), 11874–11874. https://doi.org/10.3390/ijms252211874