RIVERS STATE UNIVERSITY
PORT HARCOURT

THE BRAIN BALLOON CONUNDRUM: ODYSSEY IN QUEST FOR ANSWERS

AN INAUGURAL LECTURE

BY

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DEDICATION

In loving memory of late Miss Nechan Glenn Kibikiwa

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ABBREVIATIONS

AA	Aneurysm inclination Angle
ACA	Anterior Cerebral Artery
AHA	American Heart Association
ASA	American Stroke Association
aSAH	Aneurysmal Subarachnoid Haemorrhage
BBB	Blood Brain Barrier
BC	Before Christ
BCSFB	Blood Cerebrospinal Fluid Barrier
BMJ	British Medical Journal
CI	Confidence Intervals
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTA	Computed Tomography Angiography
DCI	Delayed Cerebral Ischemia
DSA	Digital Subtraction Angiography
EI	Ellipticity Index
FRESH	Functional Recovery Expected after Subarachnoid Hemorrhage
GABA	Gamma Aminobutyric Acid
IFAA	International Federation of Associations of Anatomists
IPD	Individual Participant Data Meta-analysis
LR	Likelihood Ratio

MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiography
NSI	NonSphericity Index
PCA	Posterior Cerebral Artery
SAFARI	Seizure Following Aneurysm Rupture
SAHIT	Subarachnoid Haemorrhage International Trialists Collaboration
UI	Undulation Index

PROTOCOL

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Heads of Departments and Units
Distinguished Professors and Members of Senate
Teaching and Nonteaching Staff
Students of Great RSU
Ministers of God
Your Royal Majesties, Highnesses and Chiefs (Alabo)
My Family Members, War Canoe House and Community
My Friends and all Invited Guests
Gentlemen of the Press
Distinguished Ladies and Gentlemen

1.0 PREAMBLE

I am highly delighted to be given the singular honour and opportunity to present the 99th Inaugural lecture of this great University. Today's lecture will mark the 4th from the College of Medical Sciences, and the 3rd from the Department of Human Anatomy. This achievement, you will agree with me, is very encouraging from our young College of Medical Sciences. It further underscores the academic strength of the Department of Human Anatomy; a department that graciously carries the College on its shoulder.

1.2 Symbolism of the number 99 to today's event

My choice as the 99th Inaugural lecturer may seem incidental. But as I reflect on the journey of my life and academic career, it dawns on me that there is a deeper significance to today's event, beyond the opportunity of sharing with this distinguished audience a snippet of my academic specialization and contributions to the advancement of human knowledge. Indeed, the number 99 is highly symbolic. In the Bible, it is associated with three thematic spiritual connotations: it symbolizes God's mercy and kindness; personal change and spiritual growth; and lastly the relevance of human or animal blood. In the parable of the lost sheep, a shepherd leaves 99 sheep to go in search of one that is lost, illustrating God's love, forgiveness and mercy, even when we stray from our path (Matthew 18:12–14; Luke

15:3–7). Today's event therefore reminds me of how privileged my life has been; of God's love, care and generosity towards me, though undeserving I might be.

Second, the number 99 also refers to the age at which Abram's name was changed to Abraham by God (Genesis 17). That change signalled a turning point for him, one of spiritual awakening and personal development in his walk with God. The journey of my academic career in some sense also reflects this theme. From the very first day I took a boat as a young academic staff of Niger Delta University in 2002, travelling almost daily on the river Nun from NDU waterfront in Yenagoa to Amassoma, Bayelsa State, I have experienced tremendous personal growth and development, which have positively shaped my attitude as an empathic teacher, seasoned researcher and community leader.

Lastly, according to Bible scholars, the word "*Blood*" is recorded 99 times in the original language of the New Testament. For today's event, the word "Blood" has literal and figurative implications. This 99th Inaugural lecture reminds me that every privilege I have been bestowed with and my personal growth and development over the years have been because of the Lamb of God who shed His blood (an event that was also celebrated in this month of April). And as we shall see, the word "Blood" also has a nexus to the topic of today's Inaugural

lecture: The Brain Balloon Conundrum: Odyssey in quest for answers.

1.3 Background and reasons for the choice of the Inaugural lecture topic

Vice chancellor, sir, the Inaugural lecture is said to be a debt a professor owes the university and community at large. In deciding on what topic to speak about, a professor may choose from one of three general themes: the professor may (1) choose a general topic from which to provide fresh and stimulating insight of relevance to the audience; (2) talk about the development of his discipline or department, especially where he occupies an endowed chair within that discipline or department; (3) focus the discussion on his research work and how the body of work has contributed to knowledge. My topic falls under the third category. The topic is timely because it will highlight a grossly underappreciated clinical entity that has profound public health relevance. In addition, I have spent a significant span of my academic career researching about the entity. I shall therefore use the opportunity in demonstrating my contributions to knowledge with respect to this entity, highlighting how my research contributions are helping to shape clinical practice at the global level.

2.0 INTRODUCTION

Vice chancellor, sir, before I launch into the crux of this

Inaugural lecture, permit me to situate my specialization in the broader context of the medical and health sciences. My discipline is human anatomy. By definition: Human anatomy is the study of the structure of the human body, and the relationship to function. The word anatomy is from the Greek word "*anatom* " meaning to cut up or to cut repeatedly ('ana'-up; 'tome'-cut) – a reference to dissection of the body of an animal (cadaver) for the purposes of study. Human anatomy, therefore, is a highly descriptive science. Among the several disciplines of the medical sciences, human anatomy is probably the oldest. I say so because in the very first chapter of the Bible book of Genesis, we find evidence referencing a distinctive attribute of the human body.

> "So God created man in his own image, in the image of God created he him; ***male and female*** created he them."
> – Genesis 1 vs. 27

Further evidence can be seen in the second chapter of this book where mention is made of some anatomical structures; for example, nostril (verse 7) and ribs (verse 21).Adams' task in the Garden of Eden, which was to give names to all things and creatures, is akin to what anatomists do – name and describe in exquisite details virtually every part and minutiae of the human body.

From antiquity, our understanding of the structural organization

of the human body has benefitted from the contributions of great minds and philosophers of old including Empedocles (490 years BC), Hippocrates of Cos (460 years BC), Aristotle (385 years BC), Michelangelo Buonarotti (1475-1564), Leonardo da Vinci (1452–1519), and Andreas Vesalius (1514-1564), the founder of modern anatomy, to mention a few. Today, advances in technology has empowered us to probe much deeper into the fundamental organization of life at the smallest structural level; thereby revolutionizing our appreciation of the wonders of the human body and how we transfer that knowledge to posterity. The importance of human anatomy as the foundation of medical sciences cannot be overemphasized. It is the pillar or cornerstone upon which every medical or health-related discipline rests. This is because an appreciation of the structural organization of the human body is prerequisite to understanding aberrations of structure and function and the applications of solutions.

Human anatomy has several subspecializations. The International Federation of Associations of Anatomists (IFAA), as cited by Watson Jacks (2023), describes eleven specialty areas of Anatomy (Table 1). The majority of my previous research work is situated in the intersection between the two specialty areas of neuroanatomy/neuroscience and clinical/surgical anatomy; hence my recognition as "*professor*

of neuroscience and clinical anatomy." Neuroscience is the study of the brain and nervous system. It is a highly interdisciplinary science encompassing several disciplines of the life sciences. Clinical anatomyis usually defined as anatomy applied to patient care. This sub discipline entails the application of anatomy knowledge to proffer solutions to clinical problems and the demonstration of how clinical problems influence human structure organization at different levels. As I shall demonstrate in this lecture, much of my previous research work has been geared towards the application of anatomy knowledge to addressingclinical challenges associated with amorphological entity I have termed the "Brain Balloon". But before I describe this clinical condition, and my research around it, permit me to invite you, Vice chancellor, sir, on a journey about the wonders of the structure of the human brain.

Table 1: The different sub disciplines of Anatomy

Discipline	Definition
Gross Anatomy	Study of anatomy at the visible or macroscopic level
Embryology/Developmental Anatomy	Study of the structural changes that cells, tissues, organs and the human body undergo from fertilization to adulthood.
Microscopic Anatomy and Cell Biology	Study of anatomy as seen under the microscope
Neuroanatomy/Neuroscience	Study of the brain and nervous system
Radiological/Imaging Anatomy	Study of anatomy as revealed from radiological images
Clinical/Surgical/Applied Anatomy	Study of anatomy as applied to clinical problemsi.e. patient care
Physical/Biological Anthropology/Forensic Anatomy	Study of the evolution and variability in structure of the human body and the adaptation to environmental stresses
Veterinary/Comparative Anatomy	Study of the similarities and differences in the anatomical structures of different species
Anatomy Education	Application of education principles and innovative techniques to the teaching and learning of anatomy
History of Anatomy /Arts in Anatomy	Study of events that shaped the evolution of anatomy/ anatomy imaging and artwork
Anatomical Services/Ethics and the Law	The application of anatomy to human interactions and society

3.0 THE HUMAN BRAIN

Vice chancellor, sir, the brain is the most complex part of the human body. It is a principal component of the nervous system of the human body (Figure1).The brain is the seat of consciousness and intelligence, it mediates our behaviours and perception of the world around us. The human brain is the only structure in the known universe that can study about itself. From a metaphorical point of view, it would appear the rest of the human body exits for the intent of aiding the brain live out its purpose. The brain is who we are.

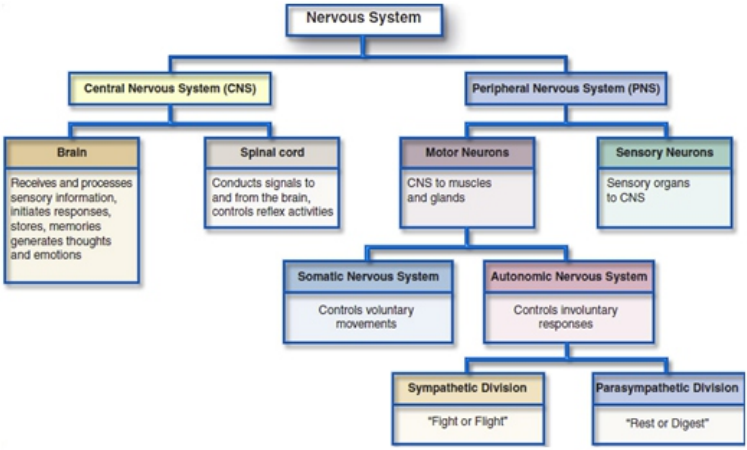


Figure 1: Schematic representation of the organization of the nervous system (Source: https://www.physio-pedia.com/index.php?curid=17983)

3.1 Gross Neuroanatomy

Viewed with the naked eye, the brain (Plate 1) is an extremely

soft, fatty organ that is protected inside the skull. It weighs, on average, 1500 grams (about 3 pounds) and accounts for just 2% of the body weight of an adult. The human brain is covered by three connective tissue membranes called meninges and floats in a small viscous fluid called cerebrospinal fluid (Plate 2). The cerebrospinal fluid supports the brain, acts as a shock absorber in rapid movements of the head, regulates the chemical environment of the brain as well as act as a channel for chemical communication within the central nervous system. The cerebrospinal fluid is located in a space between the meninges that is called the subarachnoid space. The arteries of the brain are also located in this space in close contact with the surface of the brain. The human brain has basically three parts namely: cerebrum, brainstem and cerebellum (Plate 1).

3.1.1 *Cerebrum*

The cerebrum is the largest and most visible part of the brain. It accounts for about 90% of the brain volume. The cerebrum consists of two cerebral hemispheres that are distinct halves, and each has four major components: cerebral cortex, hippocampal formation, amygdala and basal ganglia. The cerebral cortex also called the neocortex is the most developed part of the brain. It is the highly convoluted surface of the cerebral hemisphere characterized by grooves called sulci (deeper ones are called fissures), and ridges called gyri. The mean cortical surface area of the adult human brain is

approximately 2500 cm^2. The cerebral cortex has four lobes; each sub serving distinct functions(Plate 1b). The major components of the cerebrum mediate the most sophisticated of human behaviours, and they do so through complex anatomical connections with each other and the rest of the brain.

The diencephalon (meaning "interbrain") is a mass of neural tissue that lies deep within the cerebrum, generally hidden from view, and connecting the cerebrum to the brainstem. The two principal parts are the thalamus and hypothalamus. The thalamus is a paired egg-shaped structure at the middle of the brain. The primary function of the thalamus is to relay motor and sensory signals to the cerebrum. It also plays a role in regulating consciousness, sleep and emotions. The hypothalamus is located in front of the thalamus. It is the master regulator of the endocrine system, and also serves as the brain's master clock coordinating the circadian rhythm and sleep.

3.1.2 *Brainstem*

The second part of the brain called the brainstem is a stalk of tissue that connects the cerebrum to the cerebellum and spinal cord; it is continuous below with the spinal cord. The brainstem has three segments in descending order: the midbrain, pons and medulla oblongata. The brainstem servesthree general functions: (1) it receives sensory information from cranial nerves and controls the muscles of the head; (2) it serves as a conduit for information flow between the cerebrum, the spinal

cord and the cerebellum; (3) it contains centers that integrate information from a variety of sources to keep the human being in arousal (i.e., fully awake and conscious). In addition to these three general functions, each of the segments alsoserve specific functions as shown in Table 2.

3.1.3 *Cerebellum*

The cerebellum is a fascinating brain structure. Although considered to be the most primitive part of the brain, the cerebellum is so complex some experts have suggested its organization rivals that of the cerebrum. The cerebellum is located behind the brainstem in the posterior cranial fossa, and weighs just 150grams (a tenth of the weight of the cerebrum). Similar to the cerebrum, it has two cerebellar hemispheres that are thrown into folds. Within the substance of the cerebellum are collections of neural tissues called the deep nuclei. The cerebellum is divided into three functional regions, whose functions are outlined in Table 2.

3.2 Ventricular system of the brain

The brain has a tubular organization. The cavities within it comprise the ventricular system which is filled with cerebrospinal fluid. The cavity within the cerebral hemisphere is called the lateral ventricle. The cavity of the diencephalon is called the third ventricle. The fourth ventricle lies within the brainstem (pons and medulla). The interventricular foramina

connect the two lateral ventricles with the third ventricle. The cerebral aqueduct is in the midbrain and connect the third ventricle to the fourth ventricle. Cerebrospinal fluid circulates between the ventricular system and the subarachnoid space through small apertures in the fourth ventricle.

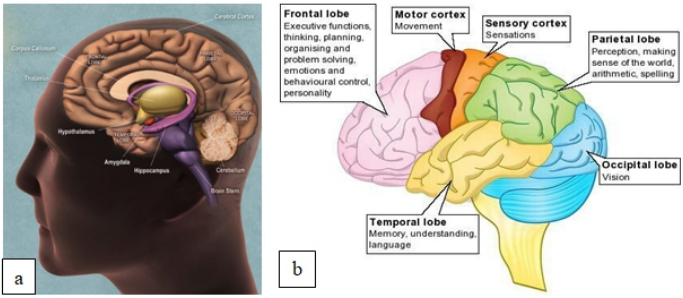


Plate 1a-b: (a) The human brain as seen within the skull; (b) A schematic diagram of the cerebral cortex showing the functions of the different lobes

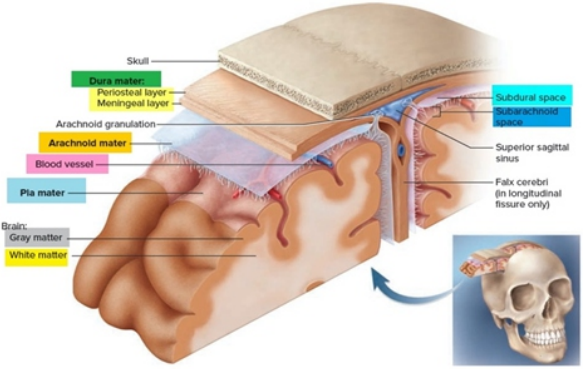


Plate 2: The coverings of the brain showing the subarachnoid space, a potential space filled with cerebrospinal fluid and in which the arteries of the brain lie in close contact with the surface of the cerebral cortex

3.3 Microscopic Neuroanatomy

Seen under a microscope, the brain has two constituent cell units: the nerve cells, also called neurons, and neuroglial cells. The neurons are about 100 billion in number, and mediate the specific functions of the brain. They come in different shapes and sizes; though each has four clearly identifiable morphological regions with specific functions, namely: dendrites, cell body, axon, and axon terminals (plate 3a). The dendrites receive information. The cell body contains the nucleus and cellular organelles critical to the survival and function of the neuron. The cell body receives information from other neurons and serves important integrative functions. The axon conducts information to the axon terminal. The axon terminal connects with the axon terminals, dendrites or cell body of other neurons via **synapsis**(plate 3b). Despite a wide range of morphology, we can distinguish three classes of neurons according to the configuration of their dendrites and axons: unipolar, bipolar and multipolar neurons (plate 3c). Unipolar neurons are the simplest and least common type; they lack dendrites. Bipolar neurons have two processes that arise from opposite ends of the cell body. There is a sub type of bipolar neurons called pseudo-unipolar neurons. Many sensory neurons such as those which transmit information about odour and touch to the brain are bipolar and pseudo-unipolar neurons.

Multipolar neurons have a complex array of dendrites and a single axon that branches extensively. Because multipolar neurons have very long axons that terminate at distant sites within the brain, spinal cord or peripheral organs, they are also called projection neurons.

Information flows within a neuron as electrical impulses in a unidirectional manner. (i.e. polarized) – from dendrites and cell body to the axon. Similarly, communication of information between neurons also is polarized and occurs at specialized sites called synapsis. The neuron sending the information is called a presynaptic neuron while the one receiving the information is a postsynaptic neuron. To send a message to its postsynaptic neuron, a presynaptic neuron releases neurotransmitter into the synapse. Neurotransmitters are small molecular weight compounds including amino acids (for example, glutamate, glycine, gamma aminobutyric acid, or GABA), acetylcholine, monoaminergic compounds such as norepinephrine and serotonin. Larger molecules such as peptides can function also as neurotransmitters, including encephalin and substance P. Although chemical synaptic transmission is the most common way of sending information from one neuron to another, direct electrical transmission also is possible as a result of cytoplasmic continuity between some pre- and post-synaptic neurons. The Neuroglial cells which form the other major constituent of the

brain provide structural and metabolic support to the neurons. They outnumber the neurons by about 10 neuroglial cells to 1 neuron, underscoring the formidable task of their functional roles. Their structure and functions are outlined in plate 4.

3.4 The Blood-Brain Barrier and Blood-Cerebrospinal Fluid Barrier

The unique structure and functions of the brain requires a stable environment in which the brain can function without disruption from other body functions. The Blood Brain Barrier (BBB) is a selective semi-permeable membrane between the blood and the substance of the brain that allows the blood vessels of the brain to regulate molecules and ions movement between the blood and the brain. The functions of the BBB are to shield the brain from toxic substances, filter harmful compounds from the brain to the bloodstream, regulate the communication between the brain and the periphery, and supply the brain tissue with nutrients. The BBB therefore maintains the homeostatic environment to allow the brain function without disruption from other bodily functions. The Blood Cerebrospinal Fluid Barrier (BCSFB) is a physiochemical barrier that separates the blood from the cerebrospinal fluid. It is formed by a tuft of tissue located in the ventricles of the brain called the choroid plexus. The choroid plexus is responsible for the secretion of CSF. The BCSFB avoids the passage of various blood-borne compounds

and selectively permits the transport of essential molecules into the brain. Compared to the BBB, the BCSFB is more permeable.

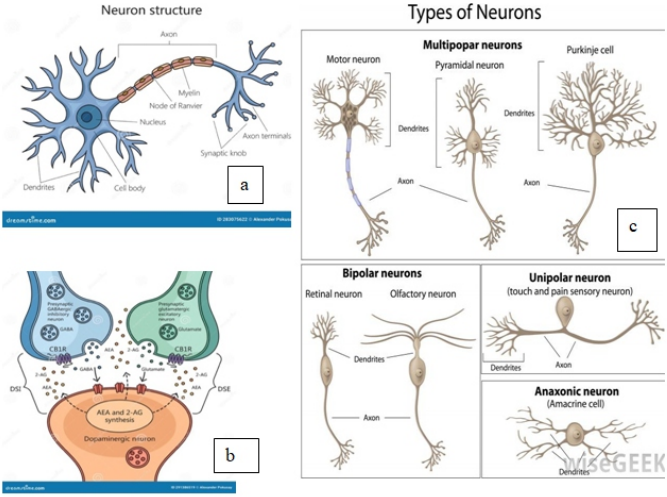


Plate 3a-c: The structure of the neuron, synapsis and the broad categories of neuron (Source: www.wisegeek.com)

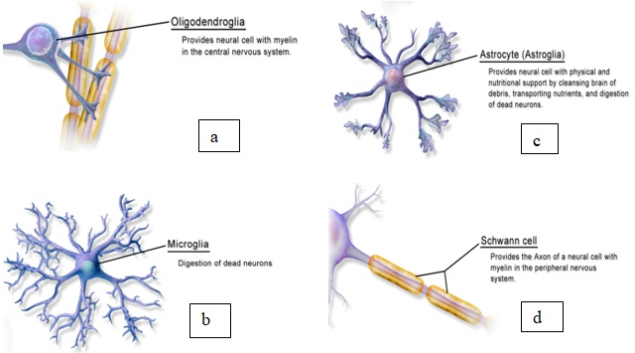


Plate 4a-d: The principal neuroglial cell types and the functional roles in the brain (*Source:www.wisegeek.com*)

Table 2: Functions of different parts of the human brain

	Cerebral Cortex	**Specific Functions**
Cerebrum	Frontal lobe	• Serve behavioural functions, from thought to action, cognition and emotions • Planning and coordination of movement
	Parietal lobe	• Mediates the perception of touch, pain and limb position
	Temporal lobe	• Perception and localization of sound • Assist with other sensory and emotional functions and memory
	Occipital lobe	• Sub serve vision
	Hippocampal formation	• Important in learning and memory
	Basal Ganglia	• Participate in cognition and emotions • Coordinate movement
	Amygdala	• Help coordinate the body's response to stressful and threatening situations • Participates in emotions
	Diencephalon	
	Thalamus	• Relay motor and sensory signals to the cerebrum • Regulate consciousness, sleep and emotions
	Hypothalamus	• Master regulator of the neuro-endocrine system • Brain's master clock coordinating the circadian rhythm and sleep
Brainstem	Midbrain	• Relay center for vision and hearing processing
	Pons	• Key role in the control of eye movement
	Medulla Oblongata	• Participate in the regulation of breathing and blood pressure
Cerebellum	Spinocerebellum	• Important in posture and limb movement
	Cerebrocerebellum	• Plays a role in movement planning
	Vestibulocerebellum	• Important in eye and head movement control

(Culled from Martin JH, Neuroanatomy text and Atlas, 2012)

3.5 Developmental Neuroscience

The development of the brain is a life-long process. It begins about two-weeks after conception and continues into young adulthood 20 years later. Recent evidence suggests the brain is capable of changing throughout the lifespan (concept of neuroplasticity), though perhaps not in every way.Brain development that occurs during pregnancy (the prenatal months) is largely under genetic control, although clearly the

environment can play a role; for example, it is well known that the lack of nutrition (e.g., folic acid) and the presence of toxins (e.g., alcohol) can both deleteriously influence the developing brain. In contrast, much of brain development that occurs postnatally (after birth) is experience-dependent and defined by gene–environment interactions.The basic structure of the brain is laid down primarily during the prenatal period (Plate 5) and early childhood, and the formation and refinement of neural networks continues over the long term. The brains' many functions do not develop at the same time nor do their developmental patterns follow the same time frame. Although basic sensation and perception systems are fully developed by the time children reach kindergarten age, other systems such as those involved in memory, decision making, and emotion continue to develop well into childhood and even adulthood.

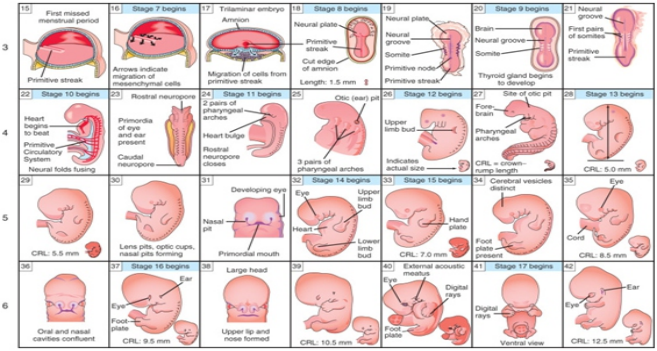


Plate 5: The stages of embryological development as seen during the first 42 days after conception (Source: https:// obgynkey.com/introduction-to-human-development/)

3.6 Functional Neuroscience

The 100 billion neurons in the human brain make over a trillion synapses with one another, and each neuron is capable of transmitting over a thousand nerve impulses, as electrical current, per second. The electrical impulses mediate the complex activities of the brain including our thought processes, most of which occur subconsciously. Cumulatively, the human brain is capable of 10^{16}information processes per second, making it far more powerful than any supercomputer in existence. The storage capacity of the human memory is believed to be limitless. The information within the brain travels at an incredible speed in excess of 250 miles per hour! The human brain is such an energy-generating powerhouse that some experts have estimated the energy output can light up a 25-watt bulb! Not surprisingly, though the brain accounts for only 2% of the body's total weight, it consumes 20% of the total energy requirement. The import of this magnitude of activity cannot be overemphasized: the human brain requires regular periods of adequate rest to replenish itself. We must be intentional in ensuring we get adequate sleep time of at least 7 uninterrupted hours every night for the optimal functioning of our brain. Because the brain is 73% water, it is very sensitive to dehydration, which affects particularly the functions of attention, memory and critical thinking. Hence, sufficient fluid

intake is recommended, especially during sunny periods of the day.

3.7 Blood supply to the Brain

Vice Chancellor, sir, it is helpful to appreciate how the brain receives its blood supply in order to more fully understand the concept of the brain balloon. There are two arterial systems that feed blood to the brain. These are the carotidand vertebrobasilar systems. The carotid systemconsists of two arteries called the common carotid arteries that run upwards along the front of the neck. One is on the left and the other on the right side of the neck. Their pulsations can be felt just under the jaw. Near the top of the neck, each carotid artery splits into two branches called the external and internal carotid arteries. The external carotid artery is responsible for supplying blood to the face and scalp. The internal carotid artery (anterior circulation) is the main artery feeding blood to the brain. Its areas of supply include most of the cerebrum, except for parts of the temporal and occipital lobes.On the other hand, the vertebrobasilar system (posterior circulation) begins as the vertebral arteries that travel upwards along the spinal column, one on each side of the column. The two arteries will join to form a single basilar artery near the brainstem along the base of the skull (hence the name vertebrobasilar system). The area of supply of this system includes the posterior aspect of the cerebrum (parts of the

temporal and occipital lobes), parts of the cerebellum and the brainstem. The carotid and vertebrobasilar systems will connect through the circle of Willis, forming an arterial loop around the brainstem at the base of the skull. From the circle of Willis, other arteries will branch off into the substance of the brain to directly supply it. These arteries include the anterior cerebral artery (ACA), middle cerebral artery (MCA) and the posterior cerebral artery (PCA). The circle of Willis ensure redundancy in the blood supply to the brain. This is fully achieved by two posterior communicating arteries that allow blood to flow between the MCA and PCA; and two anterior communicating arteries that allow blood to flow between the ACAs. Many individuals lack one of the components of this functional arterial loop, resulting in incomplete cerebral perfusion by the available system. Blood drains from the brain into a system of veins called the dural sinuses, which are located in the outermost layer of the meninges (dura matter). Ultimately, blood from the brain will return to the heart through the jugular and other veins. It is pertinent to note that because the brain relies on only two major arteries for its blood supply, all effort must be made to keep the arteries healthy. Below are 6 tips to keep the brain and its blood vesselshealthy (Plate 6).


a

Physical Exercise

Aim to exercise several times per week for 30 to 60 minutes. Take a walk, swim, play games and participate in sports, or do any other moderate aerobic activity that increases the heart rate.

Sleep


b

Aim for 7 to 8 consecutive hours of sleep per night, not fragmented sleep of two- or three-hour increments. Consecutive sleep gives the brain the time to consolidate and storememories effectively


c

Healthy Food

Emphasize plant-based foods, whole grains, fish and healthy fats, such as olive oil. Incorporate less red meat and salt. Drink plenty water to stay hydrated

Brain Exercise


d

The brain is similar to a muscle — you use it or lose it. Keep the brain in shape by playing games like crossword puzzle, sudoku; reading a book

regularly, learning new skills like playing a musical instrument, and regularly practicing meditation

Socialization


e

Social interaction helps ward off depression and stress, which can contribute to memory loss. Look for opportunities to connect with loved ones, friends and others, especially if one lives alone

No smoking


f

Only drink alcohol in moderation and don't smoke cigarette. Get your blood pressure, blood sugar and cholesterol checked regularly and take steps to keep the numbers within a normal range.

Plate 6: Tips to a healthy brain and artery
(Culled from: www.mayoclinichealthsystem.org)

4.0 THE BRAIN BALLOON: A CLINICAL ANATOMY PERSPECTIVE

Vice Chancellor, sir, for the purposes of this Inaugural lecture, I have coined the term **"Brain Balloon"** to metaphorically describe a clinical entity better known as brain aneurysm, or cerebral aneurysm or intracranial aneurysm. A brain aneurysm

is a localized swelling, bulging or dilatation (ballooning) of the wall of a blood vessel (usually an artery) in the brain. It arises as a result of weakening of the wall of the affected artery. The aetiology is obscure and very complex. However, we generally believe that they are chronic, acquired degenerative disorder of the cerebral arteries. They may arise spontaneously and sporadically or associated with individuals who have a family history of brain aneurysm. It is difficult to estimate how many people harbour an aneurysm in their brain because this morphologic entity could occur in anyone at any age, though rare in children and more common in people over age 40 years.They usually cause no symptoms; and pass undetected since we do not routinely screen for them. Nonetheless, some experts suggest that as high as 1 in 20 people (i.e. 5% of the general population) are affected by a brain aneurysm. Others suggest the numbers are much lower in the range of 1 in 100 people. We know that the prevalence of brain aneurysm isapproximately the same in all racial/ethnic groups. However, they are mostly found in women compared to men, especially when women are in the perimenopausal and menopausal period. To the general public, a brain aneurysm sounds alarming considering the risk of rupture, which could be potentially life-threatening. However, most aneurysms remain small, do not grow in size and cause no observable health challenge. Most

people who harbourabrain "balloon",are unaware of it, enjoy their live and die from other conditions. We only get to find out about their aneurysm when such individuals have a brain imaging investigation for other unrelated medical conditions or at autopsy or during cadaver dissection in our anatomy laboratories. In rare instances, an aneurysm can grow big, leak or explode (rupture) with bleeding (haemorrhage) into the substance of the brain or more commonly into the space around the brain. This event which is described as a hemorrhagic stroke or aneurysmal subarachnoid haemorrhageis life-threatening and requires emergency medical attention.

4.1 Classification of Brain Aneurysms

A number of criteria has been used in classifying brain aneurysms including the morphology of the aneurysm, the parent artery involved (location), size of the aneurysm and the geometry.

4.1.1 Morphology

In terms of morphology, six types of aneurysms are recognized, namely: saccular, fusiform, mycotic, pseudo,blister aneurysms and microaneurysms (plate 7). A saccular aneurysmalso called "Berry aneurysm" is the most common type accounting for 90% of brain aneurysms. It looks like a balloon or berry sticking out of the side of the blood vessel wall; hence it tends to have a neck attachingit to the parent artery. This aneurysm is capable of

growth and subsequent rupture spilling blood into the substance of the brain or the space around it, with potential devastating consequences. Saccular aneurysm is metaphorically a ticking time bomb.Fusiform aneurysm is less common than saccular aneurysm. This aneurysm appears as a spindle-shaped circumferential bulge of the arterial wall; hence it lacks a neck. Fusiform aneurysm is less likely to grow and rupture, but produces symptoms due to pressure on neighbouring brain structures. A mycotic aneurysm is actually a saccular aneurysm caused by infection originating somewhere else in the body (for example the heart) and spreading through the bloodstream to affect a brain artery. Understandably, the other name for a mycotic aneurysm is "infectious aneurysm". It is a rare aneurysm. A pseudo or false or dissecting aneurysm is a localized expansion of the artery that does not involve all three layers of the arterial wall. Very often, it is the outermost layer of the arterial wall that balloons out. A pseudo aneurysm is usually the result of a traumatic injury to the blood vessel wall. There is the blister aneurysm which appears like a blister on the arterial wall. This aneurysm may bleed readily and cause a higher incidence of mortality. Finally, a microaneurysm, also known as Charcot-Bouchard aneurysm, is mostly found in small arteries < 300 micrometer, particularly the lenticulostriate vessels of the basal ganglia. Microaneurysm is associated with chronic

hypertension and rupture readily.

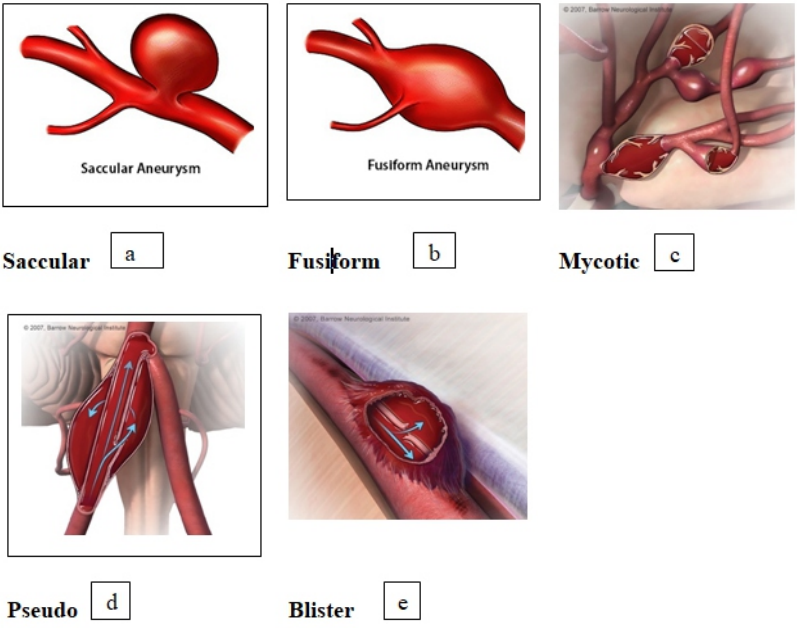


Plate 7a - e:The different morphological types of brain aneurysm (Source: Barrow Neurological Institute and Joe Niekro Foundation)

4.1.2 Location:

A brain aneurysm may be named according to the parent artery involved. Research indicatesthat 85% of saccular aneurysms arise from the arteries of the circle of Willis, typically at the point of origin. The most frequent location is the anterior communicating artery (40%), followed by the internal carotid artery, usually at or near the origin of the posterior

communicating artery; the middle cerebral artery, and finally about 15% occur in the vertebrobasilar or "posterior" circulation(Plate 8). About 20% of individuals may harbour multiple aneurysms.

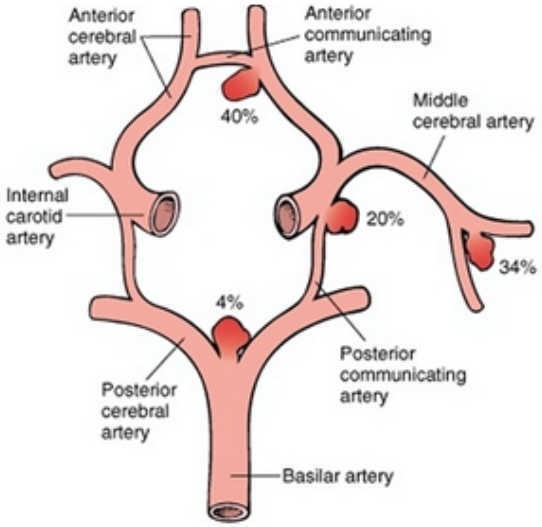


Plate 8: Prevalence of brain aneurysms by location

4.1.3 Size/Diameter:

Brain aneurysms have been commonly classified according to the size or diameter of the aneurysm into: small, medium, large or giant aneurysm. The cut-off point for categorization has varied considerably with different researchers using different size classifications. Merritt et al. (2021) proposed a classification definition for brain aneurysms based on the dome width and neck type (Table 3). The literature suggests that, on

average, unruptured aneurysms have a mean size of 5 mm compared with ruptured aneurysms (mean size 6mm).

Table 3: Aneurysm size classification based on dome width and neck type

Small	Medium	Large	Giant	Wide-neck
<5mm	5mm -10mm	>10mm -25mm	>25mm	Neck >4mm and/or DNR <2mm

DNR: Diameter Neck Ratio(*Source: Merrit et al, 2021*)

4.1.4 Geometry:

Advances in neuroimaging technology has afforded researchers the opportunity to devise new metric indices aimed at improving the extent to which we can predict aneurysm rupture. Among the many indices, the more familiar ones include the aspect ratio, size ratio, volume generated 3D morphologic metrics such as the Undulation Index (UI), Ellipticity Index (EI), Nonsphericity Index (NSI), the vessel Aneurysm inclination Angle (AA) (Figure 2), to name a few. The Aspect ratio is the ratio of the perpendicular height of the aneurysm to the neck width of the aneurysm. Aneurysms with high aspect ratios will have deep domes and small necks. Aneurysm growth and rupture can occur at areas of low wall shear stress, which are likely in aneurysms with a high Aspect ratio and deep domes. A high Aspect ratio has consistently been reported in ruptured aneurysms. Ruptured aneurysms on average have an Aspect ratio of 1.5. The size ratio is the ratio of the maximal aneurysm

height to the average parent vessel diameter. Aneurysms with high size ratios have deep domes compared with the diameter of their parent vessel. This ratio differs between ruptured and unruptured aneurysms. On average, ruptured aneurysms have a size ratio of 2.3. The size ratio is relatively larger in anterior cerebral, anterior communicating and basilar artery aneurysms. Since the size ratio accounts for the parent artery diameter, it may be a more reliable predictor of risk of rupture than the size or diameter of the aneurysm only. It is a particularly useful indicator of the risk of rupture for aneurysms < 5mm.

The Ellipticity index quantifies the degree of elongation of the aneurysm's dome in relation to a sphere,where a sphere-shaped aneurysm would have an EI of 0.The Undulation index is a measure of the degree of undulation present on the aneurysm wall surface.The NSI accounts for the degree to which an aneurysm deviates from a spherical shape by combining the EI and UI. In contrast to an unruptured aneurysm, a ruptured aneurysm tends to have higher EI and NSI. The higher NSI for ruptured aneurysm suggeststhat ruptured aneurysms are more irregular than their unruptured counterparts. Ruptured and unruptured aneurysms tend to have similar UI.

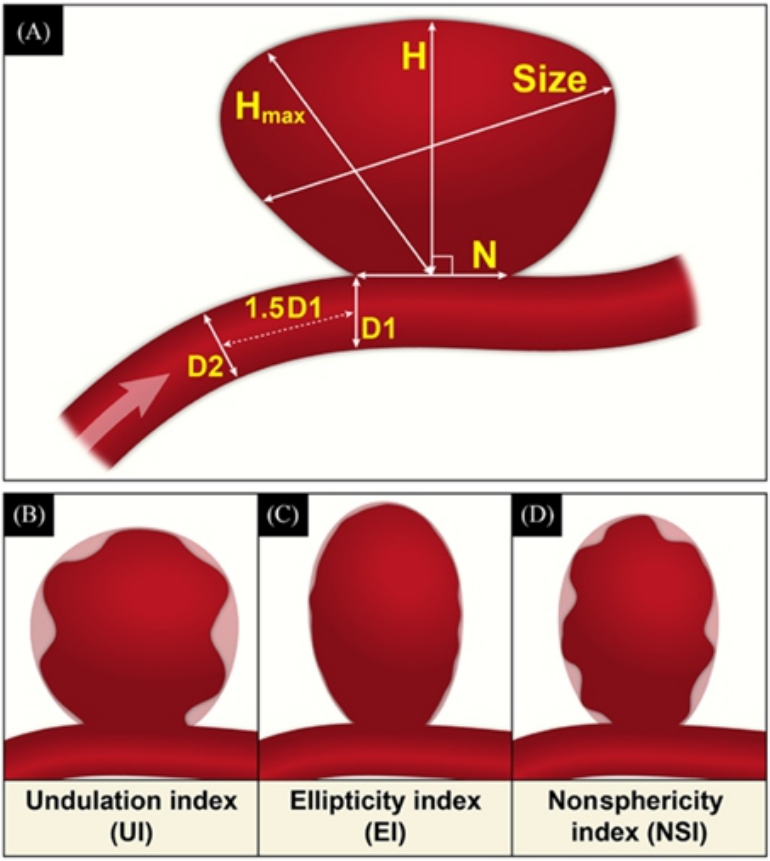


Figure 2: Illustration of geometric parameters A, Schematic representation of morphological parameters that can be manually measured. B–D, Advanced aneurysmal 3-dimensional volumetric parameters. D indicates diameter; EI, ellipticity index; H, height; Hmax, maximal height; N, neck; NSI, nonsphericity index; Size, maximal diameter; and UI, undulation index (Source: Sanchez et al. 2023)

5.0 THE BRAIN BALLOON AS A TICKING TIME BOMB

5.1 Natural History of Brain Aneurysm

As I discussed earlier, a brain aneurysm is essentially a docile clinico-morphologic entity. Over time, however, a brain aneurysm may expand and the arterial wall becomes too thin, leading to rupture and bleeding into the brain or more commonly into the subarachnoid space (Plate 9). Given the risk of rupture inherent in all brain aneurysms, this entity represents a ticking time bomb. Considerable research has gone into unravelling the processes involved in the formation, growth and subsequent rupture of an aneurysm. The research aims to identify predictors of rupture risk, a critical first step in guiding treatment choice. Particularly, the decision as to whether preventive aneurysm repair to mitigate the risk of rupture with the potential of associated neurologic complications or sequential monitoring offers optimal treatment outcome for an index case.

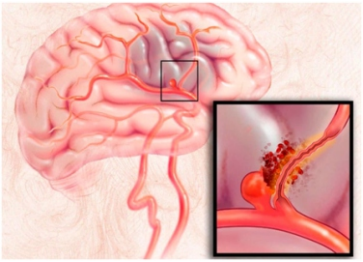


Plate 9: Schematic representation of a ruptured brain aneurysm (Source: https://www.mayoclinic.org)

The process of aneurysm development follows a common pathway that involves initial formation, progressive growth and eventual rupture. Aneurysm formation is believed to be initiated by haemodynamic stress which induces endothelial dysfunction, followed by inflammatory reaction in the arterial wall involving primarily macrophages and smooth muscle cells, and finally degradation of the extracellular matrix by metalloproteinases (Plate 10). The weakened arterial wall under continuous haemodynamic stress causes progressive outpouching of the wall, which thins out and ultimately ruptures. The role of haemodynamic stress as the initiating factor predisposing to aneurysm formation is evidenced by the observation that brain aneurysms occur at arterial junctions, bifurcations, or abrupt vascular angles where excessive haemodynamic stresses are exerted on arterial walls.Aneurysm growth is mediated by two mechanisms at interplay. One mechanism is the expansion of the wall as a result of mural cells proliferation with production of extracellular matrix, and myointimal hyperplasia. The other is distention of the wall due to haemodynamic pressure in degenerated aneurysms. Although, most brain aneurysms will grow before rupturing, many will not. The implication is that the processes driving aneurysm growth and rupture may not be entirely identical.The final rupture event may not be dramatic. In some cases, the

aneurysm simply leaks blood into the subarachnoid space causing more subtle clinical manifestations.

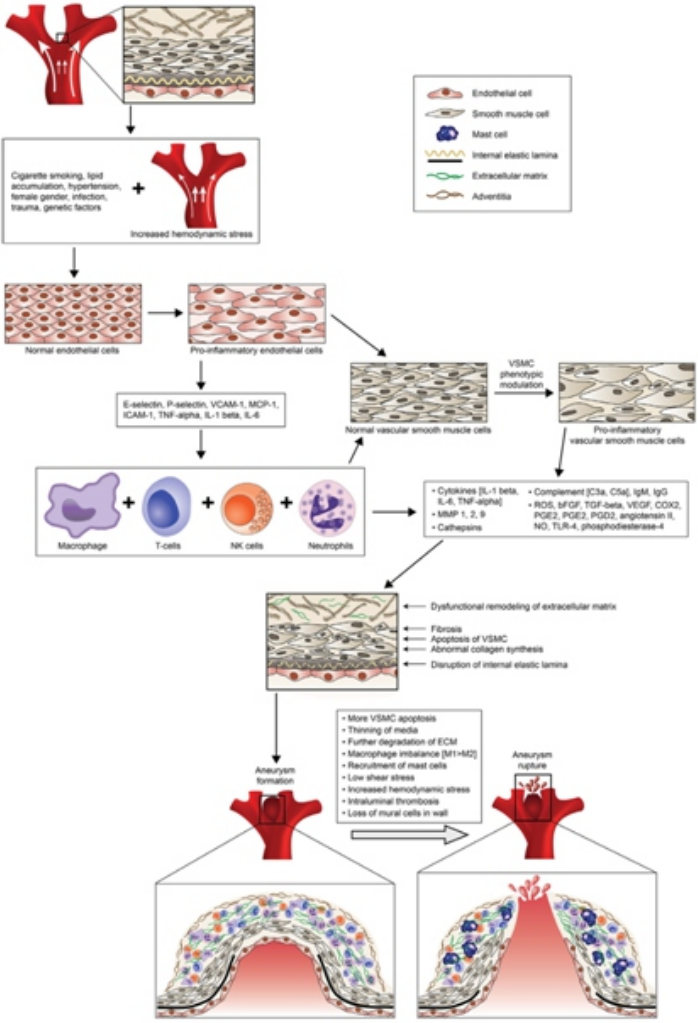


Plate 10: Mechanism of aneurysm formation and rupture

5.2 Predictors/ Risk Factors for Aneurysm Formation, Growth and Rupture

We do not know what causes brain aneurysms to develop, or why they grow in size and ultimately rupture. But researchers have identified many factors as contributory (Table 4). Many of these risk factors are inherently constitutive, therefore non-modifiable.Others are modifiable, presenting opportunities to prevent or delay the formation, growth and rupture of the aneurysm. I have broadly categorized these risk factors into those related to the individual and factors related to the anatomy of the aneurysm. Since the aneurysm-specific characteristics are inherent to the anatomy of the aneurysm, they are non-modifiable. In contrast, individual-specific factors are, to a large extent, modifiable. The later are commonly classic vascular risk factors related to behaviour and lifestyle. Of note, they are implicated in about 2/3 of individuals with brain aneurysm.

5.2.1 Individual-specific Risk Factors

5.2.1.1 Modifiable risk factors

1. ***Smoking:*** Cigarette smoking is the single most important modifiable risk factor for aneurysm development (Plate 11a). Cigarette smoking affects every step in the cascade of events leading to aneurysm formation, growth and rupture. Cigarette smoking has a dose-dependent detrimental effect.It has been shown to increase the risk of rupture 3-fold. Individuals who

harbour an aneurysm are strongly advised to quit smoking. The importance of this simple intervention cannot be overemphasized. Even in those who have had prior treatment, cigarette smoking is a risk factor for recurrence.

2. ***Hypertension:*** In addition to cigarette smoking, hypertension is a modifiable risk factor that strongly predispose an individual to aneurysm formation, growth and subsequent rupture (Plate 11b). Elevated blood pressure results to increased hemodynamic stress on the arterial wall. Therefore, blood pressure control is another simple intervention that may help to decrease the risk of aneurysm formation, growth and rupture. It is pertinent to note that the combined risk of aneurysm formation in individuals who smoke and are hypertensive increases synergistically from 3-fold for smoking or hypertension to 8-fold when both are coexisting.
3. ***Alcohol:*** Heavy alcohol consumption does not appear to be associated with aneurysm formation and growth. But it increases the likelihood of rupture. Studies suggest consumption of >150grams/weekof alcohol is associated with a 2-fold higher risk of aneurysm rupture (Plate 11c). The increased risk may be related toa

transient increase in blood pressure.

4. ***Other modifiable factors:*** Researchers have identified the use of stimulants such as coffee and cola consumption to be predisposing factors to aneurysm rupture. Additionally, anger, straining during defaecation, sexual intercourse, and even vigorous physical exercises are known triggers of aneurysm rupture. The common denominator among these factors may be the propensity to increased haemodynamic stress.

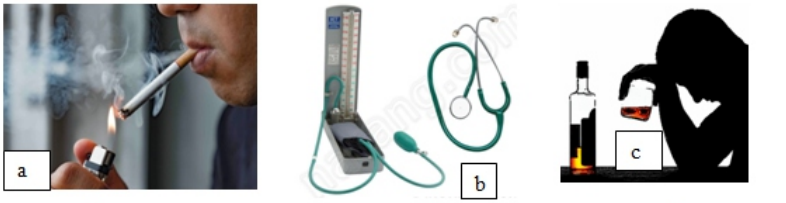


Plate 11: Important modifiable risk factors for aneurysm formation, growth and rupture

5.2.1.2 Non-modifiable risk factors

1. ***Age:*** Brain aneurysms are most prevalent in people ages 35 to 60 years, but can occur in children as well. Most aneurysms develop after the age of 40 years. The older the individual becomes, the higher the chances that the aneurysm will grow and ultimately rupture. The rupture risk is particularly higher among those 70 years and

older.

2. ***Sex:*** Women are more likely than men to develop a brain aneurysm (3:2 ratio). This preponderance is evident only in the perimenopausal and postmenopausal periods. Once formed, the likelihood of aneurysm growth is also higher in women. Also, the risk of rupture is 3-fold higher in women than men. The reason for this sex difference is uncertain, though some role has been postulated for sex hormones, particularly oestrogen. Research suggest hormone replacement therapy is protective against aneurysm rupture.
3. ***Race/ethnicity:***As earlier mentioned, the prevalence of brain aneurysm is approximately the same in all racial/ethnic groups. Finnish and Japanese populations have a lower risk of aneurysm growth and higher risk of rupture compared with European and American populations. The risk of rupture is twice higher among blacks compared with white populations.
4. ***Prior history of ruptured aneurysm:*** Individuals who have experienced a ruptured aneurysm, are at higher risk of developing a new aneurysm. The aneurysm is less prone to grow, but more likely to rupture. In essence, they rupture at a relatively smaller size.
5. ***Family History/Genetics:***There is some evidence to

suggest a genetic predisposition to brain aneurysms in selected individuals. Those with a family history in one and two affected relatives have a 2-fold and 4-fold increase in the incidence of brain aneurysm. The aneurysms are more commonly multiple and found in the middle cerebral artery, tend to be larger and rupture at a younger age, compared with those among the general population. Genome-wide linkage studies have identified a number of susceptibility loci that may contain genes implicated in familial brain aneurysms. Examples include:1p34.3-p36.13, 19q13.3, Xp22 and 7q11. The 7q11 loci contains the collagen type 1A2 gene and is adjacent to the elastin gene, both of which contribute to the structural integrity of the arterial wall. Furthermore, researchers have found 3 single-nucleotide polymorphisms associated with the presence of brain aneurysms. The single-nucleotide polymorphisms are located within the *CDKN2B-AS1* gene on chromosome 9, on chromosome 8 near the *SOX17* transcription regulator gene, and on chromosome 4 near the endothelin receptor gene. Other candidate genes that have been studies include: metalloproteinases, angiotensin-converting enzyme, phospholipase C, nitric oxide synthetase, transforming

growth factor beta, among others. Despite the extensive research, the role of genetics has not been fully established; it is more likely that familial brain aneurysm is a multifactorial process involving an interplay of genetics and environmental factors.

On the other hand, some heritable diseases of the connective tissue and extracellular matrix are associated with increased incidence of brain aneurysm. Notably, autosomal dominant polycystic kidney disease, where 10% of affected persons develop a brain aneurysm. Other hereditary diseases with a link to brain aneurysm include: Ehlers-Danlos syndrome, neurofibromatosis, and a1- antitrypsin deficiency, among others. It is important to mention that a common heritable disease in our population that has been linked to brain aneurysm is sickle cell anemia. Patients with sickle cell anemia might present with multiple aneurysms, including aneurysms in the posterior circulation. The presumed mechanism is endothelial injury due to the sickle cells.

5.2.2 Anatomic Risk Factors

Aneurysm size/diameter: The size of an aneurysm is an important predictor of growth and rupture (Figure 3). Generally, larger aneurysms are more prone to grow in size and rupture than smaller aneurysms. Giant aneurysms (>20mm) have a

disproportionately higher risk of rupture (33%) compared to small aneurysms (0.5%). Nevertheless, the average difference in size between ruptured and unruptured aneurysm is just 1.5mm. This finding indicates that aneurysms may rupture at very small size. Most ruptured aneurysms are less than 7mm. Brain aneurysmstend to remain unchanged or increase in size after rupturing. In a minority of cases, the aneurysm may shrink to a smaller size.

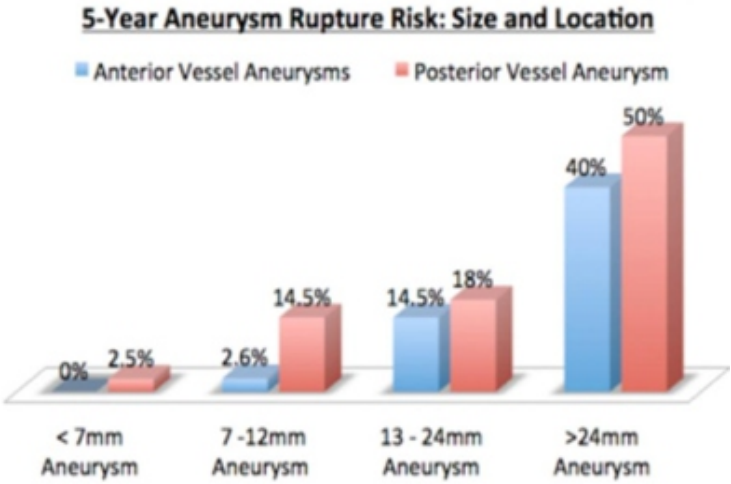


Figure 3: Aneurysm rupture risk at 5 years in relation to size and location

2. ***Parent artery involved (aneurysm location):*** Aneurysms are more commonly found in the anterior circulation with the highest prevalence in the anterior communicating artery (35-40%). Aneurysm

growth rate is higher for posterior circulation aneurysms (3.8% per year) compared with anterior circulation aneurysms (2.7%). The annual rupture rate by location has been estimated to be: 0.26% for paraclinoid, 0.67% for middle cerebral artery, 1.31% for anterior communicating, 1.72% for posterior communicating, and 1.90% for basilar artery aneurysms. This data demonstrates a higher risk of rupture for aneurysms that are located in the posterior circulation.

3. ***Shape:*** Aneurysms with irregular shape have a 2-fold higher growth rate. They are more prone to rupture as well. Examples of such aneurysms include non-saccular (fusiform) aneurysms, aneurysms with blebs, lobulations, and daughter sacs, among others. Hence, finding cues of instability in shape can aid clinicians in triaging unruptured aneurysms for treatment.
4. ***Multiplicity:*** Multiple aneurysms have a higher growth rate than solitary aneurysms(ratio 3:2). They have a 5-fold higher risk of rupture compared to solitary aneurysms.
5. ***Growth:*** Aneurysm growth occurs in 12 – 18% of individuals with a brain aneurysm during a 3 year follow up. About 45% of aneurysms will show some evidence of growth during 20 years follow up. Evidence of

growth is a predictor of further growth and rupture. In alarge study that followed 258 unruptured aneurysms with computed tomography angiography, the annual risk of rupture was found to be 2.4% in aneurysms with growth versus only 0.2% in those without growth (i.e. 12-fold increase in risk of rupture) (Villablanca et al., 2013).The risk of rupture for growing aneurysmis 3% per year compared with a nongrowing aneurysm (0.1% per year).In patients managed conservatively, periodic follow-up (every 6–12 months) with noninvasive imaging studies (magnetic resonance angiography or computed tomography angiography) is recommended. Strong consideration for elective treatment is given to any aneurysm that grows over the follow- up period given the higher risk of rupture.

6. ***Aneurysm Geometry:*** The aneurysm geometry as indicated by the aspect ratio, size ratio, among other geometric indices, has been correlated with the risk of growth and rupture. A meta-analysis of 13 025 aneurysms showed that aneurysm size of 6.1 mm, aspect ratio of 1.5, size ratio of 2.3, ellipticity index of 0.2, and non-sphericity index of 0.24 were significantly correlated with ruptured status. The aspect and size ratios are better at identifying risk of rupture for small

aneurysms (< 5mm) in the anterior cerebral artery and anterior communicating artery. An aspect ratio ≥1.5 and size ratio ≥2.3 increase the risk of rupture, independently of size.

7. ***Others:*** Other factors that may predict brain aneurysm growth and rupture include aneurysm blood flow pattern as seen in the parent vessels, flow dynamics including the flow velocities, density and viscosity, and lastly the Wall Shear Stress (defined as the force per unit area which is exerted by a solid boundary i.e. arterial wall on a fluid in motion i.e. blood and vice versa, in a direction on the local tangent plane

Table 4: The relative importance of brain aneurysm risk factors

Risk Factor	Formation	Growth	Rupture
Individual-related			
Modifiable			
Smoking	+++	+++	+++
Hypertension	+++	+++	+++
Alcohol	-	-	++
Non-modifiable			
Age	++	+	++
Sex	++	++	++
Race/Ethnicity	-	-	+
Prior History	++	-	++
Family History	++	++	++
Aneurysm-related			
Size/diameter	na	++	+++
Location	++	++	++
Irregular shape	na	++	++
Multiplicity	na	++	+++
Growth		++	+++
Geometry	na	++	++

Note: - means no associated risk; na, not applicable; + small risk; ++ moderate risk; +++ high risk

6.0 THE CONSEQUENCE OF A RUPTURED BALLOON

Vice Chancellor, sir, I have earlier mentioned that brain balloons (aneurysms) are essentially innocuous anatomic entities localized to the brain arterial wall. That they are generally symptomless and present no immediate health challenges. Nonetheless, they are prone to rupture (approximately 1% per year of affected persons). When this happens, blood spills into the substance of the brain or more commonly into the subarachnoid space. The resultant clinical entity following the blood spillage is called a haemorrhagic stroke or more commonly aneurysmal subarachnoid haemorrhage.

6.1 Significance of Aneurysmal Subarachnoid Haemorrhage (aSAH)

Vice Chancellor, sir, aSAH is a significant global public health threat. The condition is an acute cerebrovascular event which can have devastating effects in affected persons, their family members and society in general. The overall worldwide incidence is approximately 6.1 per 100,000 person-years. The global prevalence is estimated to be 8.09 million cases.

There are considerable regional variations in the incidence, with the highest incidence rates reported in Japan (26/100,000) and Finland (16/100,000).Unlike the more common ischemic stroke that occurs mostly among the elderly, aSAH occurs more

commonly in younger adults with an average age between 40 – 60 years; i.e., it generally affects individuals during their working years.

Patients who experience a ruptured brain aneurysm leading to aSAH are at high risk of death or residual brain injury;those who are fortunate to survive the condition have a lower life expectancy and quality of life than the general population. The average prehospital mortality rate is 26% in developed countries, but this rate is disproportionately higher in resource-limited climes such as ours, with inadequate prehospital care facilities including functional ambulance services. The hospital mortality rate varies widely between 8% to 67%. Most affected patients will die on the first day following the aneurysm rupture. There is some evidence that the fatality rate is falling in developed countries due to public health measures to reduce cigarette smoking, advanced neuro-preventative and timely specialized treatment services, but this trend is not seen in other climes.

Individuals who survive aSAH have varying degrees of neurocognitive andfunctional deficits which limit their capacity for independent living. Less than 1/3 ofpatients are able to return to their previous occupation and lifestyle.Only 50% of survivors were independent for activities of daily living within one year of the aneurysm rupture;i.e. they have sufficient motor

function to be able to engage in routine tasks such as bathing, shopping, among other tasks. Individuals who achieve functional independence still experience significant neurocognitive impairment including anxiety, depression, memory deficits, language deficits and deficits in executive functions i.e. critical thinking and decision making.

Attention has scarcely focused on the experience of the significant others (spouses or children) of individuals who suffer an aSAH, or on the societal burden of the condition. The grief following a loved one who dies suddenly at the most productive period in her/his life is indescribable. Family members of those who survive the condition are often burdened with the cost of care. Manyfamilymembers report experiencing symptoms of psychosocial and emotional distress, less social interactions and sleep dysfunction. Some have reported working shorter hours at their jobs or being assigned positions with less responsibilities and remuneration to allow them care for their loved one. One persistent cause of anxiety is the fear of recurrence.

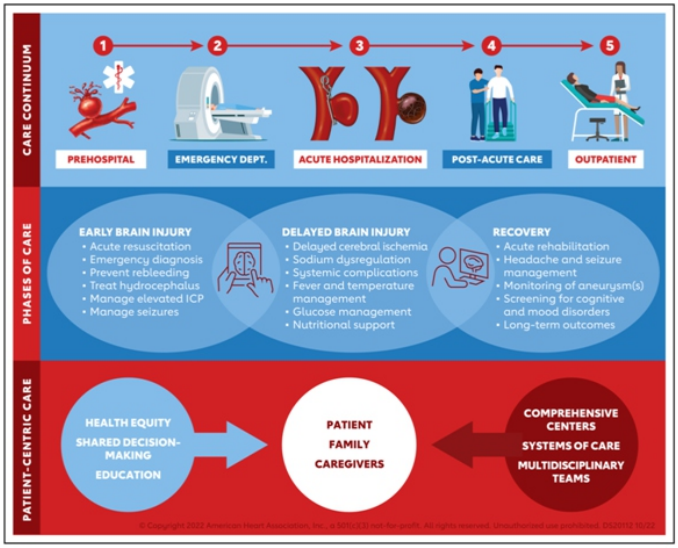
The economic burden associated with a ruptured aneurysm also is enormous and underappreciated. According to the 2023 American Heart Association/ American Stroke Association clinical guidelines, inpatient hospital charges in the United States for patients with aSAHis about $373 353.94 and as much

as $530 544.77 in those patients with aSAH who develop delayed cerebral ischemia.These costs are exclusive of post-hospitalization costs associated with long-term care and rehabilitation or the societal cost of loss of work and productivity of patients with aSAH.

6.2 Management of aneurysmal subarachnoid haemorrhage

Headache is the most common clinical manifestation of a brain aneurysm. The headache could be due to a mass effect from a large unruptured aneurysm or from a minimally leaking aneurysm that spills blood into the cerebrospinal fluid causing a raised intracranial pressure. Other symptoms include bilateral temporal hemianopsia (from an anterior communicating artery aneurysm impinging on the optic chiasm) or a unilateral third cranial nerve palsy (from a posterior communicating artery aneurysm). These symptoms could be a warning sign of an impending rupture as 10% to 45% of patients with aSAH report experiencing a sentinel headache in the 2 months preceding the rupture. A ruptured aneurysm causes a more dramatic headache called a “thunderclap headache”. The headache is sudden in onset and immediately reaches maximum intensity. Some have described it as the “worst headache of my life.” Patients also may experience nausea and vomiting, loss of consciousness, neck stiffness and seizures. On admission, 50% of aSAH patients are in deep coma.

Figure 4 shows the continuum of care for patients who sustain a ruptured aneurysm casuing a SAH.



ICP indicates Intracranial pressure

Figure 4: The continuum of care for ruptured brain aneurysm causing subarachnoid haemorrhage (Source: Hoh et al, 2023)

For those patients who are alert at hospital presentation, a workflow has been suggested to guide the clinical work-up. The Ottawa SAH Rule could serve as a tool to screen out individuals with a low likelihood of aSAH (Table 5). The work flow is intended to minimize the risk of misdiagnosis which has been reported in 20% of individuals with symptomatic brain aneurysm.Non-contrast head computed tomographic (CT) scan is the mainstay of SAH diagnosis. In suspected patients with CT negative results, xanthochromia on lumbar puncture done

preferably 12 hours after onset of headache is helpful to confirm SAH. Once SAH has been confirmed, a catheter angiography would be done to demonstrate and localize the ruptured aneurysm. However, intraarterial digital subtraction angiography (DSA) is considered the gold-standard for evaluation of cerebrovascular anatomy and aneurysm geometry to aid decision making on the choice of optimal treatment modality. Other diagnostic alternatives include computed tomography angiography (CTA) and magnetic resonance angiography (MRA), and transcranial Doppler sonography. The latter are non-invasive imaging modalities that are also more appropriate for serially monitoring of aneurysms because of the risks associated with invasive angiography.

It is important to repair the ruptured aneurysm as soon as feasible to reduce the risk of re-bleeding or aneurysm re-rupture, an event that is frequently fatal. Two treatment modalities are possible: surgical clipping or endovascular coilingof the ruptured aneurysm. The choice of which treatment to use is highly nuanced since each modality has advantages and disadvantages. Early multidisciplinary team-based approach to treatment and rehabilitation after the ruptured aneurysm is secured is recommended to improve functional outcomes and reduce hospital length of stay.

Table 5: Ottawa SAH Rule

For alert patients >15 y of age with new severe nontraumatic headache reaching maximum intensity within 1 h. Patients require additional investigation for SAH if they meet any of the following criteria:	
1	Age ≥40 y
2	Neck pain or stiffness
3	Witnessed loss of consciousness
4	Onset during exertion
5	Thunderclap headache (instantly peaking pain)
6	Limited neck flexion on examination

(Source: Hoh et al, Stroke, 2023)

6.3 Prevention of Brain Aneurysms

Vice chancellor, sir, brain aneurysms cannot be prevented. But there are measures that could be taken by the general publicto lower the risk of aneurysm formation, growth and rupture. These primary prevention strategies entail behaviour and lifestyle modifications for healthy living. As highlighted earlier, it is critical to avoid cigarette smoking and hypertension since these factors are the most important modifiable risk factors that have been implicated in 2/3 of individuals with brain aneurysms. Secondary prevention includes screening for a brain aneurysm in individuals who are at high risk. Routine screening with magnetic resonance imaging is recommendedfor individuals with a family history of aneurysm in order to facilitate early identification of the brain aneurysm.

For individuals who alreadyharbour a brain aneurysm, tertiary prevention is recommended to minimize the risk of rupture. Such individuals should preferably have preventive treatment of the aneurysm if there is evidence of progressive growth, or the aneurysm is large (>6mm) or producing pressure symptoms, irrespective of the size.

CT indicates computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; Dx, diagnosis; and SAH, subarachnoid hemorrhage Figure 5: Workflow for patients with symptoms concerning for aSAH (Source Hoh et al. Stroke, 2023)

7.0 CURRENT LANDSCAPE OF BRAIN ANEURYSM IN AFRICA

The landscape of brain aneurysm in Africa may well vary from what is obtainable globally in terms of the epidemiology, natural history, clinical manifestations, treatment and prognosis. Brain aneurysm is believed to be rare in sub Saharan Africa, but whether the low frequency reported in the region is real or due to scarcity of advanced neuroimaging services is uncertain. However, available literature indicate that the prevalence of brain aneurysm seems to be rising in Africa, with rates estimated to be doubling every 5 years, unlike in developed climes where the rates have been dropping over the last three decades. Studies suggest the preponderance of women affectation seen globally may not be the case in Africa, where the sex ratio appears to be equal. The average time from diagnosis to treatment for brain aneurysm in Africa is considerably longer compared to Western nations, with a mean time of 12.1 days in Africa compared to approximately 26 h in Western countries. Resources for advanced neuro-diagnostics and neuro-intervention are scarce. Individuals in Africa who suffer a ruptured aneurysm leading to subarachnoid haemorrhage may have a poorer prognosis. The average mortality rate in available case series is higher than reported for other climes.

With respect to research, there is a paucity of studies – one

review found no publication on brain aneurysm for nearly 80% of countries (Figure 6). Most research in the region (50% of these reported from Morocco and South Africa) where case reports or case series including rather small populations (< 100) and documenting experience from a single facility. Brain aneurysm research and management in Africa is hampered by limited availability and access to neuro-diagnostic tools which are critical for aneurysm identification, monitoring and mapping of the three-dimensional anatomy. Opportunities for mentorship and cutting-edge research also is limited in the region. Another significant challenge is the issue of inadequate funding either due to lack of financial capability or low allocation to research endeavours by governments at different levels in the region.

Figure 6: Map of Africa showing the few countries with published research on brain aneurysm (Source: Ferreira et al, 2023)

8.0 THE BRAIN BALLOON CONUNDRUM: MY QUEST FOR ANSWERS

Vice Chancellor, sir, I have devoted a significant span of my academic career so far, researching several challenging themes related to the brain "balloon". My research has been geared towards elucidating the anatomic characteristics of this clinico-morphologic entity, and how the evolving understanding could contribute to predicting the outcomes of those who sustain a ruptured aneurysm leading to subarachnoid haemorrhage. I shall summarize my contributions to knowledge in this arena under four broad thematic categories.

8.1 The Research Evidence Quality Conundrum

Vice chancellor, sir, we know a lot, yet so little about the aetiology, pathogenesis and outcomes of brain aneurysms. Though brain aneurysms are very complex entities, a major limitation to knowledge creation has been the paucity of quality studies upon which to base recommendations for clinical practice. This challenge is not unique to brain aneurysm research. Indeed, it is a prevalent challenge in the medical sciences and other disciples as well, where studies involving human populations tend to be suboptimal in terms of the size of the population sampled, representativeness/ generalizability, or methodological rigour. However, the research evidence quality challenge is particularly relevant for brain aneurysm research for a number of reasons: (1) brain aneurysms are relatively

uncommon entities, and we do not routinely screen in order to identify individuals who harbour aneurysm so as to invite them for research; (2) the neuro-diagnostic imaging tests for brain aneurysm are prohibitive in cost, their availability is often limited to specialized centres; (3)individuals who have aneurysmal subarachnoid haemorrhage are treated as an emergency, a scenario less prone to research inquest. It is therefore, not unexpected that most brain aneurysm studies, as is the scenario with other relatively uncommon clinical conditions, are based on small populations hence potentially underpowered, capture localized experiences only, and generally present conflicting evidences. The majority of brain aneurysm studies fall under the lower rung of the Evidence Level pyramid (Figure 7). Innovative paradigms to brain aneurysm research, therefore, were needed in order to more fully address the evidence quality conundrum.

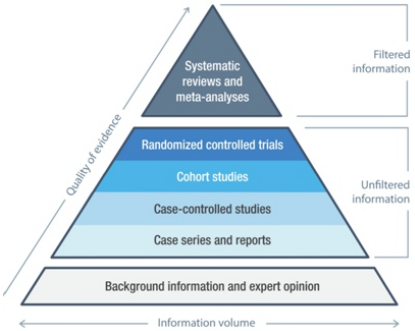


Figure 7: The Evidence Level Pyramid
(Source: https://openmd.com/guide/levels-of-evidence)

8.1.1 My contributions to resolving the challenge:

Experts from diverse background and interest in brain aneurysm research collaborated to establish a global network called the Subarachnoid Haemorrhage International Trialists Collaboration (SAHIT) (Plate 12). This international collaborative network of investigators pooled the individual patient data on ruptured brain aneurysm from different practice settings including from clinical trials and institutionally collected prospective databases under protocols approved by research ethics boards. Members of this network are from multiple disciplines (e.g., neurosurgery, neurocritical care, neurology, biostatistics, cognitive neuroscience, neuroradiology, clinical trials, information technology). The primary aim of SAHIT is to provide a unique resource for prognostic analysis to raise the evidence level for prognostic associations, design better outcome prediction models, and research novel ways for conducting and analyzing clinical trials in aSAH. Secondary aims include facilitating collaboration between international aSAH investigators, and provide a large dataset for future aSAH-related studies.My pivotal role in the formation and activities of this multidisciplinary international collaboration is probably one of my most significant contributions to knowledge. Much of the data warehousing, manipulation, and analysis were performed under my

coordination and hands-on.

The research network has giving rise to the largest repository of individual patient data on ruptured brain aneurysm in the world. The registry has a population of about 20,000 patients from America, Europe, and Australasia (unfortunately no data from Africa). The data cover a spectrum ranging from clinical, neuroimaging, laboratory, outcomes and neuropsychological information, among other data fields. The registry has served as a pivotal research milieu resulting to over 20 landmark publications in leading general medical and specialty journals including *The British Medical Journal (BMJ), Stroke, Annals of Neurology, Journal of Neurosurgery, Neurosurgery Neurocritical care*, among others. The publications have had significant impact in raising the level of evidence for prognostic associations in aSAH, resolving some conflictingfindings in the literature, and setting new agendas forfurther research.

Figure 1. Attendees of the SAHIT meeting, from left to right, included Don Ilodigwe, Anish Kapadia, George Wong, Blessing Jeja, Tom Schweizer, Benjamin Lo, Michael D. Cusimano, R. Loch Macdonald, Andrew Molyneux, Audrey Quinn, Mervyn D. I. Vergouwen, Nima Etminan, David Hasan, Peter Le Roux, Greg Hawryluk, Victoria McCredie, James Torner, Ada Louffat-Olivares, Daniel Hanggi, and Hector Lantigua.

Plate 12: Some members of the SAHIT at the inaugural meeting of the Collaboration in Toronto, ON, Canada (Source: Macdonald et al. 2013)

8.2 The Prognostic Risk Factors conundrum

Prognostic risk factors are measurable patient, disease and treatment characteristics that are associated with outcomes of a given medical condition. These factors could be multiple extending over a broad spectrum of characteristics including demographic factors such as age, sex, race/ethnicity, socioeconomic status; anatomic characteristics and markers of structural damage and disease progression or biologic markers identified from metabolomic, proteomic, genetic, genomic and epigenomic research, among other factors. Prognostic risk factors could play important roles at different positions along the continuum of the translational pathways to improved outcomes in a given medical condition. For example, they could be helpful to distinguish a group of people with a different average prognosis in order to inform and redefine the disease diagnosis, to monitor changes in disease status and treatment response over time so as to better inform treatment recommendations and individualize patient management, and potentially to lead to better understanding of pathophysiology and treatment by identifying outliers and such. Also, prognostic risk factors could be potential modifiable targets for therapeutic interventions and could serve as building blocks for prognostic models, risk scores or prognostic scores which serve a variety of roles in clinical practice and research. Furthermore, because

prognostic risk factors are potential confounders that may mask treatment effect, accurate estimation of the magnitude of their associations with outcome is fundamental to aiding the design and analysis of interventional studies, for example for optimal use of stratification or minimization randomization in the design or use of statistical adjustment in the analysis of randomized clinical trials. Researchers have investigated prognostic associations for ruptured brain aneurysms causing a subarachnoid haemorrhageso as to identify potential prognostic risk factors, and to quantify the relative magnitude of their associations with outcome. The main challenge has been that the value or relevance of several risk factors has yet to be adequately estimated. Even for widely studied conventional prognostic risk factors, considerable knowledge gap and disagreements exist in the literature.

8.2.1 My contributions to resolving the challenge:

My research has resulted into a better understanding of the prognostic value of a number of risk factors. The research was based on a global registry of patient data on ruptured brain aneurysm (SAHIT data registry). The analysis utilized the technique of Individual-Participant Data (IPD) meta-analysis. Given the unparalleled size and representativeness of the patient population studied and the analysis rigour (IPDmeta-analysis), the research provides relatively higher level of

evidence on studied risk factors than prior studies. My research covered a range of prognostic risk factors: from demographic factors such as age, sex, race, and socioeconomic status to patient clinical characteristics including role of hypertension and markers of neurologic deficits, to the role of anatomic characteristics of the aneurysm including aneurysm size, location and blood clot density, among others.

Vice chancellor, sir, permit me to highlight some of my findings with respect to prognostic risk factors in aSAH.

8.2.1.1: Prognostic value of Age and Sex

Advancing age has been shownto correlate with poorer outcomes after aSAH,but the prognostic value of age has yet to beadequately quantified. Issues remain as to the upper age limit beyond which a considerableincrease in prognosis may be expected with advancing age; an uncertainty reflected in theliterature as the use of different cut points to describe the optimal change point in the effect ofage,making comparison across studies challenging. The sex distribution of aSAH is skewedtowards a higher incidence and rupture rates of brain aneurysms in women.However,whether sex differences are present in SAH outcomes could be debated. The objective of the study was to: (1) investigate the change point in the prognostic effect of age, if any; and (2) more accurately estimate the prognostic strength of age and sex for 3-month outcomes on the

Glasgow outcome scale (GOS).

Patient-level meta-analyses were conducted involving 10951 patients to investigate univariable association between age, sex and 3-month GOS. The adjusted effects of age and sex were estimated by fitting proportional odds models to estimate prognostic associations after accounting for the effect of other prognostic factors. Nested sets of adjustment factors were sequentially included in the analyses in the order in which they are encountered in the clinical course.Restricted cubic spline function was used to study non-linearity in the effect of age; the effect of age was scaled as the odds ratio over the difference between the 75th and 25th percentiles.

Findings:

Median age was 53 years with IQR of 44-62 years. Proportion of patients who were women was 71%. Spline plots of the shape of the relationship between age and outcome demonstrated the probability of poor outcome increases with advancing age, with a steep increase in poor outcome around the age of 60-65 years; suggesting a change point around this age group though the actual age value differed somewhat with dichotomization split point of GOS (Figure 8). The fully adjusted model (Model D) estimated a 69% increase in the odds of poor outcome when patients of 62 years of age were compared with patients of 44 years of age (OR, 1.69; 95% CI: 1.59-1.81). Meta-analyses

(Figure 9) demonstrated that, overall, prognosis was relatively poorer in women compared with men (OR 1.20; 95% CI: 1.04 – 1.39). This association was not significant on full adjustment for other prognostic factors (Model D: OR, 1.04 95% CI: 0.84-1.29).

This study confirmed the overall effect of age on outcome is rather moderate. Prognosis worsens around age 60- 65 years, though presuming the effect of age to be continuous and linear was adequate. The prognostic effect of sex was negligible. In essence, though women were at higher risk of aneurysm formation, growth and rupture, the prognosis post-rupture was not related to the sex (i.e., women and men were at equal risk of a poor outcome).

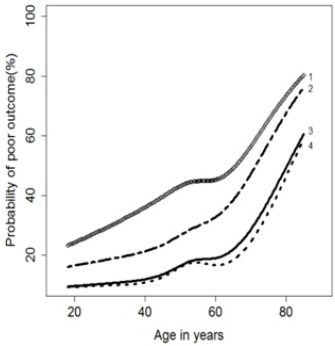


Figure 8: Spline plot of the relation of age to outcome at different dichotomization split points of the GOS

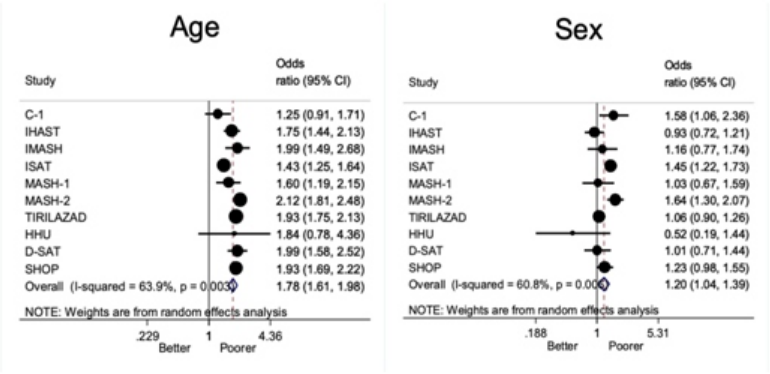


Figure 9: Forest plot demonstrating consistency across studied populations in the effects of age and sex

8.2.1.2: Prognostic value of Neurological status and Hypertension

Hypertension has been estimated as the most prevalent comorbid medical condition with estimated prevalence of 40% in some studies. Despite many studies examining the association with outcomes, no clear evidence exists as to whether hypertension independently predicts the outcome of aSAH. While older studies focused on mortality outcomes, and did not fully account for the influence of confounding factors such as patient age, more contemporary studies with better risk adjustment also reported contradictory findings. Neurological status is the single most important indicator of the severity of brain injury soon after the brain aneurysm rupture. However, accurate estimation of the prognostic value was challenging due to suboptimal study design and analysis techniques in prior

studies. So we performed a study to more accurately estimate the magnitude of hypertension and neurological status, accounting for the aneurysm anatomical characteristics among other factors. The study included 10869 patients and the analysis approach was based on IPD-meta-analysis with multivariable adjustment for confounding factors.

Findings:

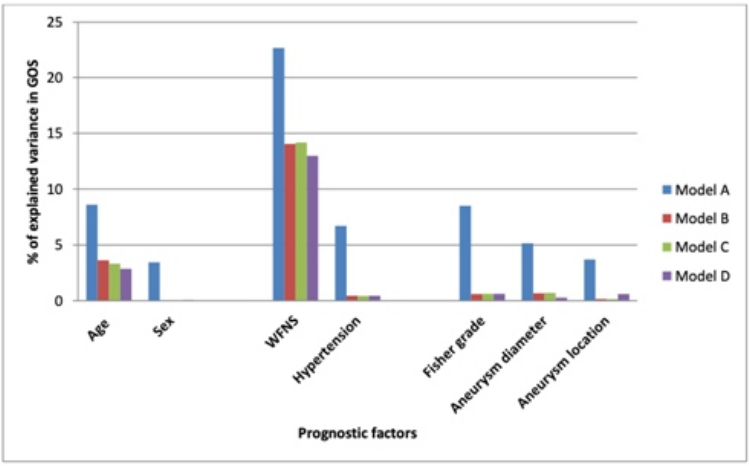
A premorbid history of hypertension was associated with poorer outcomes across the populations analyzed; the unadjusted pooled oddsratio was OR, 1.73 (95% confidence different intervals [CI]: 1.50 - 2.00). We found a strong prognostic effect of neurological status at admission. The IPD-meta-analysis demonstrated each increase in the WFNS grade resulted to approximate doubling of the risk of poor outcomes (Table 6). When prognostic strength was evaluated using the partial R2, we found neurological status was the strongest prognostic risk factor, followed by age and a premorbid history of hypertension (Figure 10). In the study, premorbid history of hypertension was associated with more severe initial bleeding, cardiovascular and renal comorbidities and complications post-ictus. The research consistent evidence across populations in support of a relationship between hypertension and poorer outcomes following aSAH. The role of hypertension may be related to the potential for hypertrophy of arterial smooth muscles and

narrowing of cerebral arteries, which could predispose to higher risk of ischemic injuries. We concluded that the findings of the study have implications for clinical management, prognosis analysis, and the design of studies evaluating novel therapies in aSAH.

Table 6: Adjusted estimates of the effect of hypertension and neurologic status

	Model A	Model B	Model C	Model D
Hypertension	1.82 (1.66 - 1.99)	1.37 (1.24 - 1.52)	1.37 (1.24 - 1.52)	1.38 (1.25 - 1.53)
WFNS I	1	1	1	1
II	2.02 (1.84 - 2.21)	1.95 (1.78 - 2.14)	1.82 (1.65 - 2.00)	1.85 (1.68 - 2.03)
III	4.65 (4.03 - 5.38)	4.19 (3.62 - 4.84)	3.86 (3.3 3 -4.47)	3.85 (3.32 - 4.47)
IV	6.62 (5.84 - 7.50)	6.12 (5.40 - 6.93)	5.56 (4.89 - 6.32)	5.58 (4.91 - 6.35)
V	17.94 (15.5 - 20.7)	18.09 (15.7 - 20.9)	15.39 (13.3 - 17.9)	14.18 (12.2 - 16.5)

Model A: Predictor (hypertension or WFNS) + Study
Model B: Model A + WFNS+Age (age only in the analysis of the effect of neurologic status)
Model C: Model B + Neuroimaging data (Fisher grade+ Artery + Ruptured aneurysm size)
Model D: Model C + Repair (clipping vs. coiling vs. conservative)



Bars represent differences in R^2 values of adjustment models with and without predictor of interest.

Figure 10: Relative prognostic value of studied risk factors expressed as Nagelkerke'sR²

8.2.1.3: Prognostic value of Aneurysm diameter, Parent artery location and clot burden

In a different study, we analyzed the aneurysm size, extravasated subarachnoid blood clot density and aneurysm location as seen on computed tomography and magnetic resonance imaging, the aim being to more accurately quantify the relationship to outcomes following a ruptured brain aneurysm. The study applied IPD meta-analysis using the data of ten thousand patients in the SAHIT registry with statistical adjustment for important confounding factors. Restricted cubic spline analysis was applied to investigate non-linearity in the effect of aneurysm diameter.

Findings:

This research demonstrated a U-shaped relationship between aneurysm diameter andoutcome, with best outcomes indicated at a diameter of 5.5mm (Figure 11). Outcomes were worse at extremes of aneurysm size, i.e., < 4 or > 9 mm. The implication is that individuals whose aneurysm rupture at very small and large sizes are at higher risk of experiencing poor outcomes. In between, aneurysm size had no relation to outcome (Odds ratio 1.03, 95% CI 0.98–1.09 for 9 mm vs 4 mm, i.e., 75th vs 25th percentile), except in those who were treated conservatively (Odds ratio 1.17, 95% CI 1.02–1.35). An interaction effect was noted between aneurysm diameter and neurologic status

($p<0.001$), and method of aneurysm treatment ($p=0.005$) but not between aneurysm size and age ($p=0.226$). An interaction was demonstrated between aneurysm location and treatment modality ($p=0.0002$) but no interaction was found between aneurysm location and neurologic status ($p=0.52$), or age ($p=0.85$).

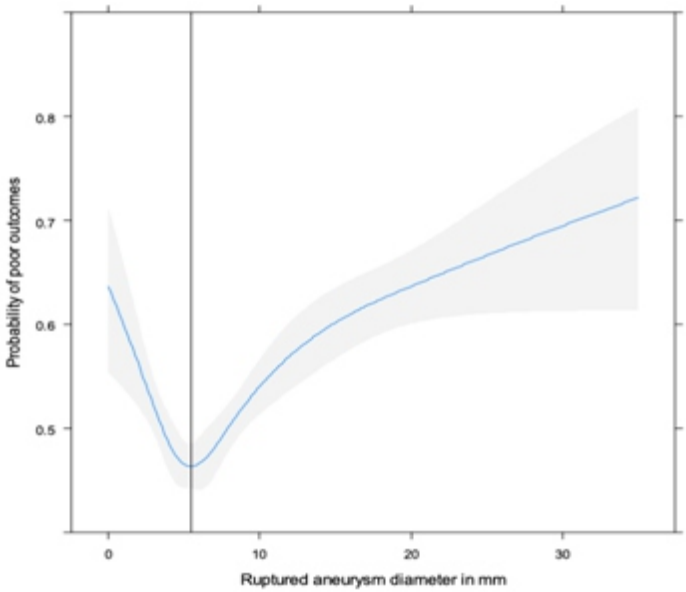


Figure 11: Spline plot shows U-shaped relation of aneurysm size to outcome with prognosis change point at 5.5mm

With respect to the parent artery, the research revealed that, compared with anterior cerebral artery aneurysms, aneurysms of posterior circulation arteries resulted to slightly poorer outcome in patients who underwent endovascular coil

embolization (Odds ratio 1.13, 95% CI 0.82–1.57) or surgical clipping (Odds ratio 1.32, 95% CI 1.10–1.57); the relation was statistically significant only in the latter.We further found the CT subarachnoid blood clot burden was related to outcome in a gradient manner (Table 7).

Table 7: Adjusted effects of anatomical characteristics

	Model A	Model B	Model C	Model D
Location: ACA	referent			
ICA	0.91(0.76-1.09)	1.01(0.91-1.12)	1.00(0.90-1.11)	0.99(0.89-1.10)
MCA	1.03(0.93-1.13)	0.92(0.81-1.04)	0.89(0.78-1.00)	0.91(0.81-1.03)
PCQ	1.17(1.04-1.32)	1.25(1.08-1.44)	1.20(1.04-1.39)	1.10(0.95-1.28)
Diameter: small	referent			
Large	1.65(1.31-2.07)	1.44(1.27-1.64)	1.47(1.29-1.66)	1.42(1.25-1.61)
Giant	2.37(1.61-3.51)	1.95(1.61-2.36)	1.97(1.63-2.39)	1.15(0.93-1.43)
Diameter (75^{th} vs. 25^{th} percentile)	1.13(1.08-1.19)	1.10(1.05-1.15)	1.09(1.04-1.15)	1.03(0.98-1.09)
Fisher grade: 1	referent			
2	1.48(1.28-1.77)	1.17(0.96-1.41)	1.21(1.00-1.47)	1.26(1.04-1.53)
3	3.29(2.79-3.87)	1.68(1.41-1.99)	1.74(1.46-2.07)	1.77(1.48-2.10)
4	3.89(3.26-4.64)	1.75(1.45-2.11)	1.79(1.48-2.17)	1.86(1.54-2.26)

NB: Data on aneurysm diameter is presented when analysed as continuous and as categorical variable
Analysis was done separately for each neuroimaging characteristic
Model A: Predictor (CT clot burden or Aneurysm location or diameter) + Study
Model B: Model A + WFNS+Age
Model C: Model B + Neuroimaging data (Fisher grade+ Artery + Ruptured aneurysm size, as applicable)
Model D: Model C + Repair (clipping vs. coiling vs. conservative

The finding of the study that outcomes are likely to be poorer in persons who present with very small aneurysms at rupture appears counterintuitive. The finding may be related to the fact that very small aneurysms have been associated with more extensive haemorrhage following rupture; a relatively higher risk of peri-procedural complications, especially following endovascular coiling embolization, hence relatively higher morbidity and mortality. Giant aneurysms present similar

challenges too. Also, some research suggests the possibility of a unique phenotype of small aneurysms characterized by an aggressive natural course and early rupture at very small sizes, leading to poor prognosis.The study further highlights the confounding role of treatment choice on the prognostic effect of the aneurysm location. It helps explain the conflicting evidence from prior literature that failed to account for treatment choice in evaluating the effect of the aneurysm location. In summary, therefore, the prognostic magnitude of the studied anatomical characteristics was rather small relative to neurological status; but they had added incremental value for predicting outcomes following aSAH.

8.3 The Outcome prediction Conundrum

Predicting the outcome of a ruptured aneurysm causing subarachnoid haemorrhage can be challenging given the considerable heterogeneity in the characteristics of affected individuals and their clinical course and the differences in the aneurysm anatomy. It is well known thatreliance on clinical intuition is grossly inadequate to accurately predict the likely course of an individual following the aneurysm rupture. Experience shows that some patients in whom outcomes were expected to be poor, have experienced a good clinical course and were eventually discharged from hospital with minimal neurologic deficits. In some others in whom the outcome was

anticipated to be good, the clinical course has been turbulent with the patient ultimately succumbing to the event. Clinical prediction models statistically combine a set of characteristics of the patient and disease to estimate the probability of an outcome. They can be useful decision support tools. Research has shown that clinical predictionmodels could help address this challenge by computing the probability of an outcome using prognostic risk factors as seen in an affected individual. These evidence-based prediction tools, according to some studies, could outperform clinical judgement in individuals with stroke. The challenge therefore has been the lack of reliable, evidence-based, user-friendly outcome prediction tools to support clinical judgement for individuals who experience ruptured brain aneurysm causing aSAH.

8.3.1 My contributions to resolving the challenge

In collaboration with other colleagues, I undertook a study to investigate whether the characteristics of the aneurysm anatomy in combination with other prognostic risk factors such as the level of neurologic deficit, hypertension, among others, could reliably predict the outcomes of aSAH (Table 8). We went further to develop a set of clinical prediction models (equations)utilizing the data from a large multinational population of patients (N=10936) to predict mortality and functional outcomes following a brain aneurysm rupture.

We evaluated the overall predictive accuracy of the models withthe R^2 statistic. Model discrimination—the ability of the modelsto differentiate between patients who did or did not have a poor outcome—was evaluated with AUC (area under the receiver operator characteristics) curves.Model calibration—the ability of the models to produce unbiased estimates of the probability of the outcome—was evaluated graphically with calibration plots (plots of observed versus predicted outcomes) and statistically by computing the following three measures of calibration: A goodness of fit test; Calibration-in-the-large; Recalibration slope. The prediction models were tested for validity in several independent cohorts(N=3355) who were treated at different regions and settings of care. The validation procedure included: Internal validation; Internal-External validation; and full external validation. A random effects model was applied to pool performance metrics across populations and heterogeneity assessed with the I^2 statistics.

Findings:

Table 9 shows the patients and aneurysm characteristics with outcomes. At internal-external validation, bootstrap resampling showed negligible model optimism. The models had internally validated AUCs between 0.77 and 0.83. There was no significant lack of fit (goodness of fit $P \geq 0.2$ inall models).The

SAHIT prediction models performed well in the pooled validation dataset and the different constituent samples. The AUC ranged between 0.76 and 0.81, indicating all models had good discrimination (Table 10).Calibration plots demonstrated agreement between predicted and observed outcomes (Figure 12). We developed an online prognostic calculator based on the prediction models' algorithms that is accessible at http:// sahitscore.com. Also available are applications for handheld devices. The SAHIT prognostic calculator computes the probabilities of mortality and functional outcomes at three months, with the associated error margins, given values of the predictor items for a patient.

The SAHITprediction tool has been a resource to support patient education and inform discussions around outcome expectations and management, including rehabilitation needs. In the outpatient clinic, doctors could use it to counsel patients with unruptured brain aneurysm about the prognosis of aneurysm rupture, and also to track the progress of recovery. In the acute care setting, the tool could facilitate evidence-informed discussions with the patient andfamily members about outcome expectations for shared decisionmaking and to facilitate timely referral to centres with theresources to provide the best outcomes.Finally, the SAHIT prediction models could be useful for research purposes and the advance of the design

and analysis of clinical trials evaluating the benefit of new therapies. For example, they could provide a more evidence-informed approach to patient selection in trials of novel treatments. My team also developed the Functional Recovery Expected after Subarachnoid Hemorrhage (FRESH) score to predict long term neurocognitive outcome after ruptured brain aneurysm.

Vice chancellor, sir, it might interest you to know that the SAHIT prediction models' article has been cited more than 200 times; many of the citations were those of studies examining the reliability of the prediction tool in different settings of care. The article has an Altimetric Attention Score of 70 indicating it is among the top 5% of all research output scored by Altimetric. Independent validation studies have confirmed the predictive accuracy of the models, and recommended the use for clinical practice (see Table 11). Recently, the American Heart Association (AHA) in conjunction with the American Stroke Association (ASA) published their 2023 Clinical Guidelines for the Management of Patients with Aneurysmal Subarachnoid Hemorrhage. Clinical practice guidelines are systematically developed statements designed to help practitioners and patients make decisions about appropriate health care for specific circumstances using the highest quality evidence from published literature that is available to support a given

recommendation. The AHA/ASA Clinical Guidelines noted that the SAHIT prediction tools and the Vasograde (see below) are useful for outcome prediction. Of note, 4 of my research papers were cited in the AHA/ASA clinical practice guidelines for aSAH.

Table 8: Definition of functional outcome endpoints

Functional outcome endpoints	Score	Definition
Unfavourable outcome	1. Death	Death
	2. Persistent vegetative state	Patient exhibits no obvious cortical function
	3. Severe disability	Patient depends upon others for daily support due to mental or physical disability or both
Favourable outcome	4. Moderate disability	Patient is independent as far as daily life is concerned. The disabilities found include degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes
	5. Good recovery	Resumption of normal activities even though there may be minor neurological or psychological deficits

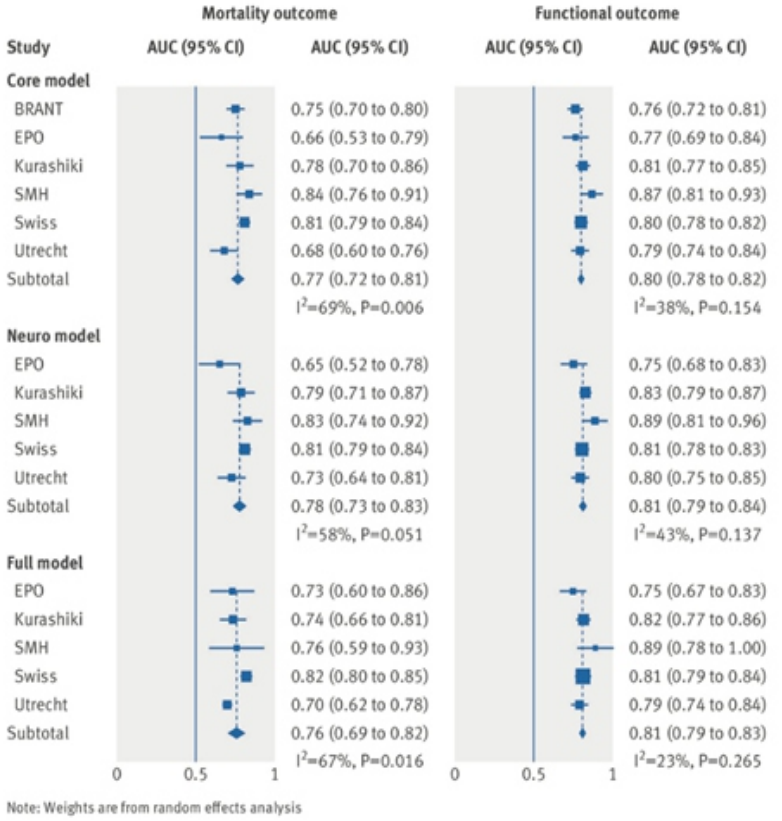
Scores and definitions for Glasgow outcome scale

Table 9: Shows the Association of patient and aneurysm characteristics with outcome following aSAH

Predictor	Outcome (%)		Odds ratios (95% CI)				Partial R^2 (%)
	Mortality	Unfavourable	Univariable	Core model	Neuroimaging model	Full model	
Age (years)	—	—	1.82 (1.72 to 1.92)	1.65 (1.56 to 1.75)	1.59 (1.50 to 1.68)	1.55 (1.44 to 1.64)	1.9
Hypertension:							
No	544 (12)	1094 (25)	—	—	—	—	0.4
Yes	522 (21)	956 (38)	1.73 (1.57 to 1.90)	1.29 (1.16 to 1.44)	1.31 (1.17 to 1.46)	1.32 (1.18 to 1.47)	
WFNS grade:							
I (good grade)	206 (4)	674 (14)	—	—	—	—	12.0
II	239 (9)	668 (26)	1.83 (1.66 to 2.01)	1.79 (1.62 to 1.97)	1.66 (1.51 to 1.84)	1.69 (1.53 to 1.87)	
III	130 (18)	325 (44)	3.78 (3.20 to 4.46)	3.44 (2.93 to 4.03)	3.19 (2.72 to 3.74)	3.18 (2.71 to 3.72)	
IV	293 (26)	594 (53)	5.93 (5.13 to 6.84)	5.35 (4.70 to 6.09)	4.81 (4.21 to 5.49)	4.73 (4.14 to 5.41)	
V (poor grade)	444 (46)	683 (71)	13.06 (11.30 to 15.09)	12.75 (10.83 to 15.01)	10.83 (9.14 to 12.84)	9.81 (8.29 to 11.61)	
Location:							
Anterior cerebral artery	317 (10)	916 (28)	—	—	—	—	0.1
Internal carotid artery	313 (12)	705 (27)	0.98 (0.88 to 1.08)	—	0.98 (0.88 to 1.09)	0.96 (0.87 to 1.07)	
Middle cerebral artery	188 (12)	450 (28)	1.06 (0.95 to 1.18)	—	0.83 (0.74 to 0.94)	0.86 (0.76 to 0.96)	
Posterior circulation	180 (18)	339 (34)	1.27 (1.11 to 1.45)	—	1.08 (0.94 to 1.24)	0.97 (0.84 to 1.13)	
Size:							
≤12	628 (9)	1801 (26)	—	—	—	—	0.1
13-24	266 (21)	465 (36)	1.51 (1.35 to 1.69)	—	1.26 (1.12 to 1.41)	1.22 (1.08 to 1.37)	
≥25	174 (36)	227 (47)	2.34 (1.87 to 2.94)	—	1.75 (1.39 to 2.19)	1.21 (0.95 to 1.54)	
Fisher grade:							
1	37 (5)	74 (10)	—	—	—	—	0.7
2	79 (5)	233 (15)	1.22 (1.00 to 1.49)	—	1.24 (1.01 to 1.52)	1.27 (1.03 to 1.56)	
3	766 (16)	1649 (33)	2.55 (2.11 to 3.09)	—	1.72(1.41 to 2.08)	1.72 (1.41 to 2.09)	
4	236 (13)	676 (38)	3.11 (2.53 to 3.83)	—	1.97(1.61 to 2.40)	2.00 (1.63 to 2.45)	
Treatment:							
Clipping	712 (10)	1881 (26)	—	—	—	—	1.3
Coiling	166 (7)	579 (25)	1.16 (1.06 to 1.26	—	—	1.14 (1.03 to 1.26)	
None	439 (52)	511 (60)	5.09 (4.19 to 6.17)	—	—	2.66 (2.21 to 3.21)	

WFNS=World Federation of Neurosurgical Societies.

Table 10: Performance of the SAHIT prediction models in the validation cohorts



Note: Weights are from random effects analysis

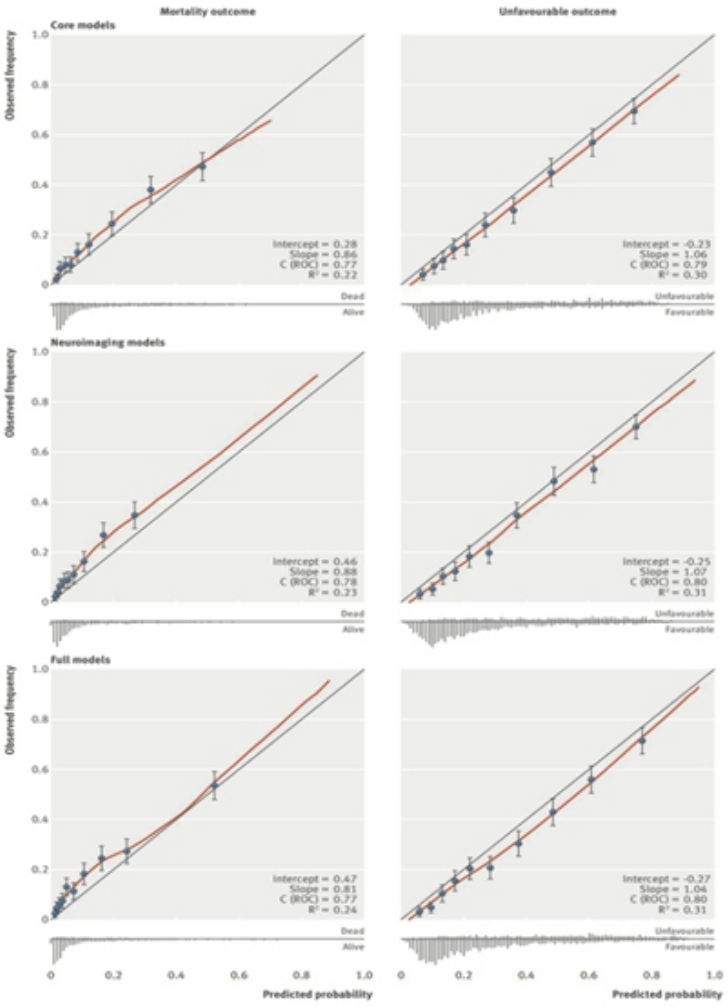


Figure 12: Calibration plot of the SAHIT Prediction Models in the validation cohorts (Source: Jaja et al, 2018)

Table 11: Some independent critical reviews and conclusions of validation studies of the SAHIT prediction models

Published Literature	Critical commentary on SAHIT prediction models
Wartenberg et al, 2019 Gap analysis regarding prognostication in neurocritical care: a joint statement from the German Neurocritical Care Society and the Neurocritical Care Society	• "The two more recently developed models, the Functional Recovery Expected after Subarachnoid Hemorrhage (FRESH) score and the Subarachnoid Hemorrhage International Trialists (SAHIT) score aim at prediction of long-term functional outcome and are considered to be the most comprehensive [24,25,26]." • "Newer prognostic models such as FRESH score and SAHIT score offer more precise long-term functional outcome prediction and are externally validated."
Mascitelli et al, 2020 External validation of the subarachnoid hemorrhage international trialists (SAHIT) predictive model using the barrow ruptured aneurysm trial (BRAT) cohort.	• "Overall, all models showed good calibration, and the measures of calibration fell within 95% CI of those produced in the SAHIT study." • "Using the BRAT data, we have externally validated the SAHIT model for predicting unfavorable outcome and mortality after SAH. The model may be used to counsel patients and families on prognosis following aneurysmal SAH."
Hostettler et al, 2020 Assessment of the subarachnoid hemorrhage international trialists (SAHIT) models for dichotomized long-term functional outcome prediction after aneurysmal subarachnoid hemorrhage in a United Kingdom multicenter cohort study	• "We assessed the performance of the SAHIT models in predicting long-term outcome after aSAH and have demonstrated adequate prediction by their good discriminative abilities in a large UK cohort. Accuracy of the SAHIT models in our cohort was acceptable measured by an AUC of 0.71, 0.73 and 0.74 of the core, neuroimaging and full model, respectively." • "We successfully demonstrate that the SAHIT models accurately predict long-term functional outcome after aSAH, measured by the dichotomized GOS at 2 years in a multicentre cohort."
Simon-Pimmel et al, 2021 Methodological quality of multivariate prognostic models for intracranial haemorrhages in intensive care units: a systematic review	• "We thus only retained the SAHIT score[41] (figure 3). In a single external validation,[42] it predicted an unfavourable outcome (mRS 3–6) or mortality at 6 months, based on clinical predictors (age, history of hypertension and WFNS preoperative neurological grade) and CT (Fisher grade, aneurysm size and location). It revealed good discrimination and calibration." • "We have chosen to emphasize the ICH score, the max ICH score and the SAHIT scores for their superior prognostic performances. Nevertheless, they need ongoing validations, recalibrations and impact studies to improve them."
Gaastra, 2022 Outcome after aneurysmal subarachnoid haemorrhage (Doctoral dissertation, University of Southampton)	• "The best available model is the Subarachnoid Haemorrhage International Trialists' (SAHIT) prediction tool which was[59] developed and validated in 10936 and 3355 patients respectively. The full SAHIT model uses commonly available demographic, clinical and imaging variables (age, World Federation of Neurological Surgeons [WFNS] score, previous hypertension, size and location of aneurysm, treatment modality, Fisher grade) to predict dichotomised clinical outcome as assessed by the GOS (GOS 1-3 versus 4-5) at 3 months post-haemorrhage. The externally validated model achieved good discrimination with a maximum area under the receiver operator characteristics[59] curve (AUC) of 0.81."
Parekh et al, 2023 Clinical prediction models for aneurysmal subarachnoid hemorrhage: a systematic review update	• "Notably, the SAHIT model showed the most extensive external validation by six independent investigators, using data from both randomized trials [19,16] and observational population-based cohorts." • "Despite the improvement in the frequency with which models were externally validated, the overall methodological quality of the models remained a concern, with a high risk of bias observed in all cases except for the SAHIT model. " • "The SAHIT model stood out due to its robust methodical quality, in that it was based on a large number of patients, using variables based on the literature and a previously performed systematic review, considered non-linear terms and interactions, reported on model performance, and was externally validated. "

8.4 The complications conundrum

Almost all patients who are in admission for a ruptured brain aneurysm develop one or more
complications during the inpatient course. The major complications include delayed cerebral ischemia, seizures, vasospasm, hydrocephalus, medical complications, and re-bleeding. My research focused on delayed cerebral ischemia and seizures.

8.4.1 Delayed Cerebral Ischemia (DCI)

For individuals who survive the initial aneurysm rupture, DCI is a major concern. DCI occurs in about 30% of patients and is seen as the occurrence of focal neurologic impairment of unknown cause, mostly between 4 to 14 days after the aneurysm rupture. It is often associated with narrowing of the cerebral arteries (vasospasm). DCI is the most important predictor of cerebral infarction, which increases the risk of poor outcomes 5-fold.

8.4.1.1 My contributions to knowledge

A number of studies were undertaken to shed light on this phenomenon. First, westudied sex and hormonal differences on the risk of DCI using information in the SAHIT registry. The research demonstrated that women are at higher risk of DCI than men, and that sex differences may play a role in the pathogenesis of DCI and cerebral infarction but not through the

mediation of menopausal status (Table 12). The study further showed that the risk factors for DCI include the extent of neurologic deficit, extravasated blood clot burden, age and sex (Table 13).However, the extent of neurologic deficit, the blood clot burden, parent artery of the aneurysm and aneurysm diameter predicted the likelihood of a cerebral infarction (Table 13).

Table 12: Effect of hormonal status on DCI and infarct

Variable	Median Age in Yrs (IQR)	DCI*	p Value	Infarctions*	p Value
Women					
≤55 yrs	45 (39–50)	Reference		Reference	
>55 yrs	65 (59–72)	0.87 (0.74–1.02)	0.08	1.01 (0.82–1.24)	0.93
Men					
≤55 yrs	44 (37–50)	0.75 (0.62–0.90)	0.002	0.81 (0.64–1.03)	0.09
>55 yrs	61 (57–68)	0.72 (0.59–0.90)	0.003	0.96 (0.73–1.25)	0.76

* Data are presented as OR (95% CI).

Table 13: Multivariate analysis to identify independent predictors of DCI and cerebral infarct

Variable	DCI*	p Value	Infarction*	p Value
Age	1.00 (0.98–1.01)	0.025	1.00 (0.99–1.01)	0.662
Female sex	1.38 (1.09–1.74)	0.007	1.02 (0.81–1.30)	0.842
Hypertension	1.06 (0.86–1.31)	0.5803	0.91 (0.72–1.13)	0.377
WFNS grade		<0.001		<0.001
I	Reference		Reference	
II	1.87 (1.40–2.49)		1.74 (1.27–2.38)	
III	3.05 (1.89–4.93)		3.05 (1.82–5.13)	
IV	3.03 (2.28–4.02)		3.28 (2.42–4.44)	
V	2.04 (1.44–2.88)		3.84 (2.73–5.41)	
Fisher grade		<0.001		0.003
1	Reference		Reference	
2	0.89 (0.53–1.50)		2.38 (1.37–4.15)	
3	1.97 (1.22–3.18)		2.48 (1.44–4.26)	
4	1.51 (0.89–2.54)		2.94 (1.66–5.22)	
Aneurysm location		0.07		0.059
ACA	Reference		Reference	
ICA	0.79 (0.61–1.01)		1.22 (0.93–1.59)	
MCA	0.82 (0.62–1.08)		0.79 (0.58–1.07)	
PC	0.67 (0.48–0.94)		1.11 (0.79–1.54)	
Aneurysm diameter (mm)		0.466		0.003
0–12	Reference		Reference	
13–24	1.23 (0.88–1.72)		1.59 (1.14–2.21)	
≥25	0.98 (0.58–1.68)		1.79 (1.10–2.92)	
Aneurysm treatment		0.303		0.354
Clip	Reference		Reference	
Coil	0.87 (0.67–1.14)		0.88 (0.66–1.16)	

* Values are presented as OR (95% CI).

In a different study, we investigated individuals who had DCI but without angiographic evidence of vasospasm (arterial narrowing). The aim was to identify risk factors for this subset of DCI. Interestingly, no risk factors were demonstrated.

In another study, we further showed that accounting for volume of intraventricular blood could improve DCI risk prediction using the modified Fischer scale for quantifying extravasated blood clot burden.

Finally, we carried out another study aimed at developing and validating a prediction tool for DCI that could be used in the hospital setting as an adjunct to clinical judgement (Table 14). The tool is called the Vasograde. It combines the extravasated blood clot burden and extent of neurologic deficit to predict DCI during hospital admission (Table 15). The Vasograde could assist clinicians with decisions on tailoring their monitoring strategies for DCI, how long to keep a patient in hospital post-aneurysm repair, and the aggressiveness of treatment in a patient who has ruptured brain aneurysm. The Vasograde also has been independently tested and validated, and also mentioned in the AHA/ASA clinical practice guideline for use in the clinical setting.

Table 14: The Vasograde for DCI risk stratification

VASOGRADE	WFNS	Modified Fisher scale
Green	1-2	1-2
Yellow	1-3	3-4
Red	4-5	Any

Table 15: Accuracy metrics of the Vasograde in a validation cohort

VASOGRADE	Sensitivity, %	Specificity, %	Correctly Classified	LR+	LR–
Green	100	0.00	21.6	1	...
Yellow	63.5	57.6	58.9	1.49	0.63
Red	49.1	74.7	69.2	1.94	0.68

LR: Likelihood ratio

8.4.2 Convulsive Seizures

About 5% to 10% of individuals with ruptured brain aneurysm have convulsive seizure during hospital admission. These individuals are at higher risk of other complications, they also tend to stay longer in the hospital and experience poorer outcomes. As a result, many centres routinely administer anticonvulsive medication for the prevention of seizures to all patient with aSAH. Others reserve anticonvulsive medication for individuals who are at high risk for seizures during the admission course. The challenge, however, is how to identify those individuals who may be prone to convulsive seizure during the hospital admission.

Table 16: Prognostic strength of predictors and the associated SAFARI score points

Predictor	OR (95% confidence intervals)	Points
Age ≥ 60 yr: No	1	0
Yes	2.68 (1.64-4.35)	1
Onset seizure: No	1	0
Yes	5.75 (3.43-9.62)	2
Hydrocephalus: No	1	0
Yes	2.46 (1.51-3.99)	1
Location: posterior	1	0
Anterior	2.77 (1.28-5.99)	1

Note: OR: odds ratios. SAFARI score has a range of 0 to 5 points. A patient who is 60 yr or older (1 point) had ruptured middle cerebral artery aneurysm (1 point), had seizure prior to admission (2 points), and presented with hydrocephalus requiring drainage (1 point) will have the maximum score of 5 points and should be considered at high risk for seizure during hospitalization.

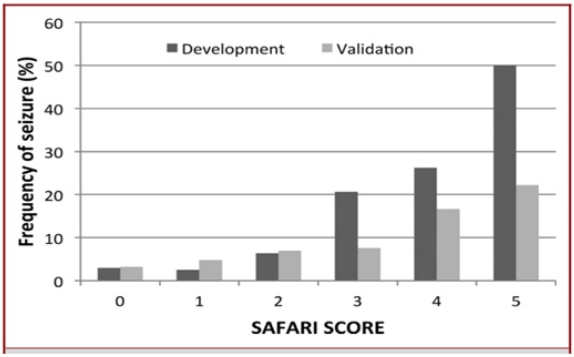


Figure 13: Proportion of patients who developed a seizure during hospitalization in the development cohort vs the validation cohort according to the SAFARI score.

8.4.2.1 My contributions to resolving the challenge

We undertook research with the aim to investigate whether the anatomical profile of the brain aneurysm could be an indicator of the risk of seizure when combined with the clinical profile of a patient. The data of 1500 patients were analyzed. The research demonstrated that the parent artery of the aneurysm in combination with other characteristics including a prior history of seizure, hydrocephalus and age reliably identify at-risk individuals (Table 16). Given this result, we developed a risk stratification tool for early identification of at-risk patients during the hospital admission (Figure 13). The tool was named the SAFARI score (Figure 13). In a validation study including 852 patients from different practice setting, we found the SAFARI score had good predictive accuracy. The SAFARI scoring system also has been independently validated by other researchers and found reliable for use in different care settings. The scoring system is particularly useful in settings without the resources to ensure continuous monitoring for seizure during admission using electroencephalograms, including most of sub Saharan Africa.

9.0 CONCLUSION

The brain is an intriguing and enigmatic organ. The very arteries that provide it with nourishment may, for unknown reasons, develop an aneurysm that might grow unpredictably and

potentially rupture with dire consequences for the health of the individual. Considering the sporadic nature of brain aneurysm and the universal risk for the general population, attention to the modifiable risk factors management is critical to minimize the prospect for aneurysm formation, growth and rupture. Simple, user-friendly, validated tools are available to support clinical decision-making about prognosis for individuals who experience a ruptured aneurysm causing subarachnoid haemorrhage. These tools have now been recommended as reliable for application in clinical practice in accord with current evidence-informed best-practice guidelines, which signposts their potential to significantly impact the continuum of care in brain aneurysm.

10.0 RECOMMENDATIONS

1. **Need to strengthen healthcare infrastructure and diagnostic capabilities:** Resources must be allocated to establish and sustain robust health systems including specialized facilities that are dedicated to specialized care and to cutting-edge applied research in the medical sciences. Such facilities would house modern diagnostic technology such as digital subtraction angiography (DSA) and advanced MRI machines, among other technologies, that are relevant to exploring

the phenotype characteristics of brain aneurysm, among other research agenda, in Africa, and Nigeria in particular.

2. **Need to foster international collaborations for research and improved management:** Fostering robust international collaborations is crucial to improving the research and treatment paradigm for brain aneurysm in Africa. Opportunities to participate in international collaborations will enable the conduct of original research specific to the African region; create awareness about the unique biology of brain aneurysm in Africa; facilitate knowledge and skills transfer, and support among researchers. Participation in international collaborations offers African scientists and healthcare practitioners the invaluable opportunity for continuous improvement and ensures high-quality care and research output. Fostering international collaboration should be a collective responsibility encompassing efforts of individual researchers, the university and the region's university systems to actively seek opportunities for linkages with institutions – both governmental and non-governmental – within and outside the continent.

3. **Need to create Public Awareness and Patient**

involvement: The creation and implementation of educational programs is crucial to improving public awareness about brain aneurysms. Public awareness is invaluable in equipping the general public with the understanding required to manage their risk profile and bolster confidence in the healthcare management of the condition. The public and individuals who have survived the condition could also participate in setting the research and healthcare agenda through the formation of support groups and foundations, as is obtainable in developed climes.

4. **Need for improved funding:** The success of the above recommendations is tied to improved funding for research and healthcare delivery in Africa. In this regard, the university and the region's university systems and governments at different levels should be intentional in the establishment of robust funding networks and initiatives to breach the huge gaps in research. Researchers should seek out for training and funding opportunities; while institutions should improve on scholarship and grants and develop modern healthcare delivery and research infrastructure.

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