



A Study of Collateral and Morphometric Correlation of Anatomical Variations in the Circle of Willis and Internal Carotid Artery in Acute Stroke in Elderly Subjects

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KEYWORDS

Circle of Willis, anatomical variations, stroke, elderly, magnetic resonance angiography, morphometric analysis, asymmetry index, Indian population

ABSTRACT:

Background

The Circle of Willis (CoW) is a great architectural wonder that ensures adequate cerebral perfusion through collateral circulation. Anatomical variations in the CoW are common and may influence stroke susceptibility and outcomes, particularly in elderly populations. Despite global research, limited data exist on the association between CoW variations and stroke in the Indian geriatric population.

Objectives

This case-control observational study aims to assess the association between anatomical variations in the Circle of Willis and internal carotid artery (ICA) with acute stroke in elderly Indian subjects (≥ 60 years) using Time-of-Flight Magnetic Resonance Angiography (TOF-MRA). Additionally, the study will develop a novel Asymmetry Index (AI) for vessel dominance assessment.

Methods

A total of 134 participants (67 cases with stroke and 67 age- and sex-matched controls) aged ≥ 60 years will be recruited from Datta Meghe Medical College and JNMC hospitals, Nagpur. TOF-MRA will be used to identify and classify CoW variations. Morphometric parameters, including vessel diameters, lengths, and asymmetry ratios, will be measured. Statistical analysis will determine associations between anatomical variations and stroke occurrence.

Expected Outcomes

The study will provide region-specific data on CoW variations in elderly Indians, establish correlations between anatomical variations and stroke risk, and introduce a novel Asymmetry Index for clinical application in stroke risk assessment.

INTRODUCTION

The Circle of Willis is a great architectural wonder of human neuroanatomy. It is a sophisticated network of interconnected arteries that acts as a vital hemodynamic interface, ensuring adequate cerebral blood circulation. This intricate circulatory system serves as a highly developed natural collateral mechanism. It offers the cerebrovascular network exceptional resilience and adaptation ((1). The Circle of Willis or circulus arteriosus is an anastomotic ring constituted by

anastomosis of two internal carotid arteries (ICAs) and the basilar artery at the base of the brain(2,3)

A six-sided polygon of arteries is formed by anastomosis of branches of the basilar and internal carotid arteries. It is formed by:

Anteriorly- the anterior communicating and anterior cerebral arteries

Posteriorly- the basilar artery, which divides into two posterior cerebral arteries



Laterally on each side by the posterior communicating artery connecting the internal carotid artery with the posterior cerebral artery

The carotid arteries and their branches supply blood to the frontal part of the brain. This is the anterior circulation. On the other hand, the posterior circulation refers to the vertebrobasilar system, which nourishes the brain's posterior region. The CoW's component vessels are the anterior communicating arteries (AcomAs) and posterior communicating arteries (PcomAs). They have been identified as the main collateral routes(1-4)

The blood flow to various parts of the brain is equalised by the cerebral arterial circle. There is little exchange of blood between the right and left sides of the arterial circles because the blood pressure is equal(3)

Since Thomas Willis provided the first thorough description of the Circle of Willis in the 17th century, it has historically captivated anatomists and neurologists (5). Originally thought of as a homogeneous artery ring, recent studies have gradually demonstrated the wide range of architectures present in this neurovascular configuration. The Circle of Willis for each individual is a distinct topographical landscape with subtle but notable changes that can have a major effect on cerebral hemodynamics (6).

Stroke represents a significant global health challenge. It ranks as a primary cause of mortality and morbidity in developed nations. Its impact is increasingly felt in low- and middle-income countries (LMICs)(7,8). Approximately 70% of strokes occur in LMICs, resulting in a disease burden. This surpasses that of high-income countries. Recent increases in life expectancy in India, which now exceed sixty years (8). This has contributed to a rise in age-related non-communicable diseases, including stroke. Consequently, stroke has become the fourth most common cause of mortality and the fifth most common cause of disability in India(8). The yearly incidence of stroke in India was estimated to be between 105 and 152/100,000 individuals in a recent systematic review, which primarily included cross-sectional studies (8,9)

Magnetic Resonance Angiography (MRA) is an attractive and non-radiation-dependent procedure for imaging of the intracranial vasculature. MRI TOF, MRI using the time of flight (TOF) technique, specifically

designed to visualize the blood vessels of the circle of Willis(10). It is a detailed 3D image of the circle of Willis obtained by a non-invasive MRI method that considers blood flow dynamics to highlight the vessels (11)

TOF MRI considers the difference in signal intensity between rapidly moving blood and stationary tissues, allowing for high-contrast visualization of blood vessels without the need for contrast dyes.(12) This scan is used to assess abnormalities in the circle of Willis, such as aneurysms, stenosis (narrowing), or any other variations in the anatomy that can lead to disturbance in blood flow. The 3D reconstruction of the TOF scan provides a comprehensive view of the circle of Willis, including its major components (13)

Functional Significance

The Circle of Willis serves multiple critical functions:

Collateral Circulation: It provides alternative pathways for blood flow in case of vessel occlusion

Pressure Equalization: it balances blood pressure across different cerebral territories

Hemodynamic Reserve: it maintains adequate perfusion during physiological variations

Neuroprotection: it minimizes ischemic damage during vascular compromise

The anterior circulation (carotid system) supplies the frontal regions of the brain, while the posterior circulation (vertebrobasilar system) nourishes posterior brain structures. The communicating arteries (AComA and PComA) serve as primary collateral routes [1-4].

History:

Thomas Willis provided the first comprehensive description of this arterial circle in the 17th century, revolutionizing our understanding of cerebral vasculature [5]. Initially conceptualized as a uniform arterial ring, subsequent research has progressively revealed the remarkable diversity of architectural patterns within this neurovascular configuration. Each individual's Circle of Willis represents a unique topographical landscape with subtle yet clinically significant variations that can profoundly impact cerebral hemodynamics [6].



Stroke: A Global and National Health Challenge

Global Burden

Stroke represents one of the most significant global health challenges, ranking as a primary cause of mortality and morbidity in developed nations, with its impact increasingly felt in low- and middle-income countries (LMICs) [7,8].

- Approximately 70% of strokes occur in LMICs
- Disease burden in LMICs surpasses that of high-income countries
- Stroke is a leading cause of long-term disability worldwide

Stroke in India

Recent increases in life expectancy in India (now exceeding 60 years) have contributed to a rise in age-related non-communicable diseases, including stroke [8].

It is the Fourth most common cause of mortality and the fifth most common cause of disability in India

Incidence: 105-152 per 100,000 individuals annually [8,9]

Age Factor: Increasing prevalence in elderly populations

The aging demographic structure of India necessitates focused research on stroke risk factors and predisposing anatomical variations in the geriatric population.

Anatomical Variations of the Circle of Willis

Prevalence of Variations

Contemporary research has demonstrated that the "complete" or "classic" Circle of Willis is present in only a minority of individuals. Studies report:

Complete CoW: 20-50% of population

Incomplete CoW: 50-80% of population

Variations more common in posterior circulation

Types of Variations

Common anatomical variations include:

1. Hypoplasia: Underdevelopment of vessel segments (diameter <1 mm)
2. Aplasia: Absence of vessel segments
3. Fenestration: Division of a single vessel into two channels
4. Duplication: Presence of duplicate vessels
5. Asymmetry: Significant difference in vessel caliber between sides

Most Commonly Affected Vessels:

- Posterior communicating arteries (PCoMA) - most frequent site
- Anterior communicating artery (ACoMA)
- Posterior cerebral artery (PCA) segments
- Anterior cerebral artery (ACA) segments

Clinical Significance

Anatomical variations of the CoW have been associated with:

- Altered stroke risk and severity
- Differential outcomes following vessel occlusion
- Aneurysm formation susceptibility
- Variable responses to endovascular therapy
- Differences in collateral flow capacity

Imaging Modalities: TOF-MRA

Magnetic Resonance Angiography (MRA)

Magnetic Resonance Angiography represents an attractive, non-radiation-dependent procedure for imaging intracranial vasculature [10,11].

Time-of-Flight (TOF) Technique: TOF-MRA is specifically designed to visualize the Circle of Willis by:

Exploiting differences in signal intensity between rapidly moving blood and stationary tissues

Providing high-contrast vessel visualization without contrast dyes, generating detailed 3D reconstructions of vascular anatomy [12]



Review:

Title	Author, Year	Study Objectives, design, and sample size	Conclusions by Author	Remarks by scholar
Stroke in India: A systematic review of the incidence, prevalence, and case fatality (8)	Stephanie P Jones Et.al International Journal of Stroke 2022, Vol. 17(2) 132 –140 © 2021 World Stroke Organization DOI: 10.1177/17474930211027834 journals.sagepub.com/home/ws	To find quality prospective studies detailing India's stroke epidemiology Systematic Review 9 Epidemiological studies of the incidence and prevalence of stroke in India included	To guide stroke policy and inform the development and organization of stroke services, more high-quality evidence is needed throughout India.	High-quality evidence is required for the development and organization of stroke services and to guide stroke policy throughout India. Methodological Gap
Association of Circle of Willis variants with stroke and aneurysm: insights from a tertiary hospital in Ethiopia(14)	HashimeMeketaNegatieet al. BMC Neurol . 2025 Feb 22;25(1):73. doi: 10.1186/s12883-025-04082-y. 2025 PMID: 39987018 PMCID: PMC11846220	The study's goals were to evaluate the structural variations of the CoW in the Ethiopian population displaying neurological symptoms and to investigate the factors associated with these changes. 86 participants facility-based cross-sectional study	The posterior part of the CoW has a higher prevalence of hypoplastic arteries than the anterior part. There is a substantial correlation between female sex and stroke and the CoW's incompleteness.	This study investigates the factors linked to these variants in the Ethiopian population that presented with neurological complaints. Aim of current study the association of variations of CoW and the internal carotid artery with stroke in the Indian population. The study is done by CT angiography we aim to do it by MRI angiography



				Methodological Gap
Circle of Willis variants and their association with outcome in patients with middle cerebral artery-M1-occlusion stroke (15)	Laura P. Westphal Et. Al 07 July 2021 https://doi.org/10.1111/ene.15013 PMID: 34233384 PMCID: PMC8596978 DOI: 10.1111/ene.15013	Magnetic resonance angiography in time of flight (TOF-MRA) Acute middle cerebral artery (MCA)-M1 blockage in 193 stroke patients Retrospective data analysis This study investigated the prevalence and distribution of CoW variations in a cohort of people who had an LVO stroke and a transient ischemic attack (TIA), as well as the impact of CoW variants on stroke clinical outcomes.	Incomplete CoW was present in 72.6% (n = 53) of TIA patients and 82.4% (n = 159) of stroke patients. More variations in the posterior circulation. There is no proof that CoW variations are related to clinical outcomes in individuals with LVO stroke who are getting EVT.	A study conducted in Switzerland in stroke patients receiving endovascular therapy. Our goal is to use TOF MRI-based case-control observational research on stroke and TIA patients in the Indian community. Methodological Gap
Evaluation of Circle of Willis variants using magnetic resonance angiography(16)	Volkan Kızılgöz Et.al. Sci Rep 2022 Oct 20;12(1):17611. doi: 10.1038/s41598-022-21833-w	867 individuals These patients' MRA pictures were acquired using the three-dimensional time-of-flight technique, which measured the vessel diameters of each COW component and classified the variations in the COW. Observational cross-sectional study (retrospective)	Statistically significant difference between entire, partially complete, and incomplete circulations between the male and female populations was observed. Small percentage of the complete circle was seen in males. The male population exhibits greater diversity. Classification and vessel parameters are also completed.	All patients who had undergone cerebral MRA for various purposes were taken into account. Our goal is to research stroke and TIA sufferers. In Indian population Methodological Gap



MRA-based evaluation of anatomical variation of circle of Willis in adult Pakistanis(17)	Rehana Shaikh et.al J Pak Med Assoc.2018 Feb;68(2):187-191 PMID: 29479090	135 subjects Cross-sectional descriptive study To ascertain how frequently and in what patterns persons without cerebrovascular disease exhibit normal anatomical variation of the Circle of Willis on MR angiography	30 (22.2%) had a complete circle, 82 (60.7%), and 23 (17.1%) had imperfect and partially complete circles. The structure varies among Pakistani individuals any symptoms of cerebrovascular illness.	Adults from Pakistan without symptoms of cerebrovascular illness participated in the study. Our goal is to investigate the association between stroke patients' variations in the circle of Willis and the Indian population. Methodological Gap
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Research Gap Analysis and Novel Criteria:

1. Morphometric Analysis and Vessel Asymmetry Ratio: measurement of arterial diameters, lengths, and asymmetry ratios will be calculated to determine hypoplasia or aplasia in posterior communicating arteries, anterior communicating artery, and other components of the circle of Willis.
2. Novel Asymmetry Score (AI): A comparison of the ratio of both sides will be done, and an asymmetry Score will be developed
3. Collateral Circulation Assessment: Grading functional completeness of the circle of Willis as complete or incomplete.

1. Methodological Gap

Novel Asymmetry Score (AI) is a novel and current method for evaluating asymmetry or hypoplasia in cerebral vessels that lacks any such type of score.

Research Question:

1. Do anatomical variations in the Circle of Willis and internal carotid artery have an association with acute stroke in elderly patients in the Indian subjects?
2. Can an Asymmetry Score be developed?

FINER Format –

F – Feasibility: Study is feasible with available resources using imaging data MRI (TOF) from elderly patients in India. Sample size, technical tools, and expertise in radiological and anatomical interpretation are accessible.

I – Inquisitive: The association between anatomical variations in the Circle of Willis and stroke is of significant interest to neurologists, radiologists, anatomists, and public health professionals, especially in elderly patients.

N – Novel: Global studies exist, but limited data are available on this association specifically in the Indian



geriatric population, making this study regionally and demographically novel.

E – Ethical: study can be conducted ethically with appropriate institutional ethical committee (IEC) approval

R- Relevant: The study addresses a critical health concern—stroke—in elderly subjects. Understanding anatomical predispositions can aid in early detection, preventive strategies, and personalized healthcare planning

Aim: The study aims to assess the association between anatomical variations in the Circle of Willis and the internal carotid artery with acute stroke in elderly Indian subjects.

Collateral correlation: Studies have documented the structural variations without integrating collateral and morphometric assessments and their impact on stroke susceptibility. It is s

It is still not clear whether these variations occur at similar frequencies across different racial populations. This study aims to assess the association between anatomical variations in the Circle of Willis and the internal carotid artery with acute stroke in elderly Indian subjects by MRI angiography.

Morphometric Analysis & Vessel Asymmetry Index:

- Measurement of arterial diameters, lengths, and asymmetry ratios to determine the extent of hypoplasia or aplasia in anterior communicating arteries, posterior communicating arteries (PCoA), and other CoW components.
- Comparing the internal carotid artery (ICA) between both hemispheres to assess the dominance of one side over the other.

Objectives:

1. To identify and classify variations in the anatomy of the Circle of Willis and internal carotid artery in elderly individuals using Time-of-Flight (TOF) MRI angiography.
2. To investigate the relationship between the variations of CoW and the internal carotid artery in the elderly (≥ 60 years) using MRI angiography and the prevalence of stroke.

3. To assess the correlation between the Circle of Willis and internal carotid artery variations to stroke risk factors in the elderly.

4. To perform morphometric analysis of the Circle of Willis and internal carotid artery in elderly individuals with stroke

5. To develop a novel Asymmetry Index (AI) Score for vessel dominance assessment in the Circle of Willis.

Methodology:

Study Design: Case-control observational study

Study Setting: The study will be conducted in the Department of Anatomy and Radiology of Datta Meghe Medical College and JNMC, Nagpur (hospital setting)

Study Duration: 2 years.

Case: Individuals aged ≥ 60 years with a history of stroke.

Control: Age- and sex-matched individuals **without stroke**

Sample Size:

The sample size calculation for a case-control study investigating the association between aneurysms and an incomplete Circle of Willis (CoW). The calculation is based on the assumption of an odds ratio (OR) of 3.2, with 50% prevalence of exposure (incomplete CoW) in the control group (14)

Odds ratio (OR)- 3.2

Design: Two-sided comparison of two independent proportions with equal allocation (1:1).

Assumptions/Inputs:

Significance level (α , two-sided)	0.05
Power ($1-\beta$)	0.90
$Z_{\alpha/2}$	1.96
Z_{β}	1.282
p_1 (Group 1 proportion)	0.7619
p_2 (Group 2 proportion)	0.5000

**Formula:**

$$n \text{ per group} = \frac{((Z\alpha/2 + Z\beta)^2 \times [p_1(1-p_1) + p_2(1-p_2)])}{(p_1 - p_2)^2}$$

Substitution:

$$p_1(1-p_1) = 0.7619 \times 0.2381 = 0.181408$$

$$p_2(1-p_2) = 0.5000 \times 0.5000 = 0.250000$$

$$[p_1(1-p_1) + p_2(1-p_2)] = 0.431408$$

$$(p_1 - p_2)^2 = (0.7619 - 0.5000)^2 = 0.068592$$

$$(Z\alpha/2 + Z\beta)^2 = (1.96 + 1.282)^2 = 10.507657$$

$$n \text{ per group} = 66.0881 \rightarrow \text{rounded up to } 67 \text{ per group}$$

$$\text{Total sample size} = 2 \times 67 = 134$$

Study Population:

Case Group: Individuals aged ≥ 60 years with a history of stroke

Control Group: Age- and sex-matched individuals without stroke.

Inclusion criteria: Individuals aged ≥ 60 years who underwent MRI for acute stroke.

Gantt Chart:

Activities	July24- Dec24	December 24-june25	June 25- Dec25	December 25-Jan26	June 26- Dec26	December 26-June 27	June 27- Dec27
Literature review							
Selection and finalization of research topic							
Writing a synopsis							
Submission of synopsis							
DRC							
Submission of synopsis to IEC							
IEC clearance and initiation of study							
Conduct of study							
Publication of protocol							
Publication of the systematic review							
Report writing							

Exclusion criteria: Individuals with a history of head trauma, craniotomy, or craniectomy, as well as those diagnosed with vasculitis, will be excluded, as this may affect the normal physiology of the circle of Willis.

Study Tool/Imaging Modalities:

MRI Angiography (TOF-MRA & 4D Flow MRI) for vessel morphology and dominance.

Data Collection:

Morphometric Parameters like vessel diameter, asymmetry indices, and variations will be recorded and statistically analyzed.

Anticipated New Knowledge Generation:

The study will aid in the development of asymmetry scoring that will contribute to the role of vessel symmetry in cerebral circulation.

This study will provide collateral and morphometric correlation of Anatomical variations in the circle of Willis and internal carotid artery in acute stroke in the elderly subjects in the Indian population.



Publication of the original article							
Submission and Presentation of Thesis							

Publication Plan:

Publication of Protocol 1, Systematic Review and Original Article 3, research articles related to project 1 or 2, will be done in the Scopus / PubMed / WOS indexed journal.

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