DIAGNOSTIC ACCURACY OF MR CAROTID PLAQUE IMAGING COMPARED WITH HISTOPATHOLOGY IN PATIENTS WITH SYMPTOMATIC CAROTID ARTERY STENOSIS

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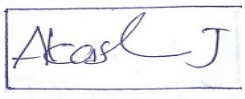
DECLARATION

I hereby declare that the work presented in my thesis titled Diagnostic accuracy of MR carotid plaque imaging compared with histopathology in patients with symptomatic carotid artery stenosisis is the result of my original research efforts and has not been submitted, in part or in whole, for the award of any other degree or diploma. I affirm that all sources used for reference and citation in this thesis have been duly acknowledged and cited in the appropriate manner.

I sincerely appreciate the guidance, support, and mentorship provided by Dr. Sylaja PN (Professor and HOD), Dr. Sapna Erat Sreedharan (Professor), Department of Neurology, Dr. Anoop A (Additional Professor), Department of Imaging Sciences and Interventional Radiology, Dr. Deepti (Additional Professor), Department of Pathology, Sree Chitra Institute for Medical Sciences and Technology and Dr Jissa VT, Achutha Menon Centre for Health Science Studies throughout the research process. Their expertise and insights have been invaluable in shaping the outcome of this work. No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.



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*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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CERTIFICATE

This is to certify that the work incorporated in this thesis titled ***Diagnostic accuracy of MR carotid plaque imaging compared with histopathology in patients with symptomatic carotid artery stenosis*** *for the degree of* ***DM NEUROLOGY*** *has been carried out by* ***Dr. AKASH J*** *under our supervision and guidance. The work done in connection with this thesis has been carried out by the candidate himself and is genuine.*

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ABBREVIATIONS

- **1.5T** 1.5 Tesla
- **2D** 2 Dimensional
- **3D** 3 Dimensional
- **3T** 3 Tesla
- **ADC** Apparent Diffusion Coefficient
- **AHA** American Heart Association
- **BMT** Best Medical Treatment
- **CAD** Coronary Artery Disease
- **CAS** Carotid Artery Stenting
- **CEA** Carotid Endarterectomy
- **CI** Confidence Interval
- **CKD** Chronic Kidney Disease
- **CT** Computed tomography
- **CTA** Computed tomography angiography
- **DWI** Diffusion Weighted Imaging
- **ECA** External Carotid Artery
- **EPI** Echo Planar Imaging
- **ESC** European Society of Cardiology
- **EVG** Elastic Van Gieson stain
- **GBCA** Gadolinium Based Contrast Agents
- **GBD** Global Burden of Disease
- **GE** General Electric
- **H&E** Haematoxylin and Eosin stain
- **HDL** High Density Lipoprotein-Cholesterol
- **HR-MRI** High-resolution Magnetic Resonance Imaging
- **ICA** Internal Carotid Artery
- **IMT** Intima Medial Thickness
- **IPH** Intra Plaque Hemorrhage
- **IS&IR** Imaging Sciences and Interventional Radiology
- **LDL** Low Density Lipoprotein-Cholesterol
- **LRNC** Lipid Rich Necrotic Core
- **MAT** Masson's trichrome stain

- **MCA** Middle Cerebral Artery
- **MES** Micro Embolic Signals
- **MMP2** Matrix Metallopeptidase 2
- **MP-RAGE** Magnetization-Prepared Rapid Acquisition With Gradient Echo
- **MRA** Magnetic resonance angiography
- **MRI** Magnetic Resonance Imaging
- **NASCET** North American Symptomatic Carotid Endarterectomy Trial
- **PACS** Picture Archiving And Communication System
- **PD** Proton Density
- **PET** Positron emission tomography
- **POVD** Peripheral Occlusive Vascular Disease
- **QSM** Quantitative Susceptibility Mapping
- **ROC** Receiver Operating Characteristic Curve
- **ROI** Region of Interest
- **SCTIMST** Sree Chitra Institute of Medical Sciences
- **SD** Standard Deviation
- **SNAP** Simultaneous Non-contrast Angiography and intraPlaque hemorrhage imaging
- **SNR** Signal To- Noise
- **SWI** Susceptibility Weighted Imaging
- **T1-SPACE** T1-weighted sampling perfection with application of optimized contrasts using different flip angle evolution
- **TG** Triglyceride
- **TIA** Transient ischaemic attack (TIA)
- **TOF** Time of Flight
- **US FDA** United States Food and Drug Administration
- **ZIP** Zero Interpolation Filli

ABSTRACT

DIAGNOSTIC ACCURACY OF MR CAROTID PLAQUE IMAGING COMPARED WITH HISTOPATHOLOGY IN PATIENTS WITH SYMPTOMATIC CAROTID ARTERY STENOSIS

Background and Aim: The MR carotid plaque imaging using 3T MRI can identify the high-risk plaques and help in deciding on need of carotid intervention and may predict periprocedural ischemic events. We evaluated the diagnostic accuracy of MR carotid plaque imaging in identifying the plaque vulnerability and compared with histopathological findings in patients with symptomatic carotid stenosis.

Methods: Forty five consecutive patients with moderate to severe stenosis who underwent carotid endarterectomy (CEA) and had 3T MRI plaque imaging with multi-sequence protocol (T1, T2, Time of flight, Diffusion, Proton density weighted and T1-postcontrast) were analysed. Images were analysed by neuroradiologist who was blinded to histopathological data. The high-risk plaque characteristics such as lipid rich necrotic core (LRNC), intraplaque hemorrhage (IPH), thin fibrous cap and ulceration were assessed and compared with histopathological findings as per American heart association (AHA) classification.

Results: The mean age was 65$\pm$7.7 years (males 84.4%) and the mean duration of CEA from recent event was 57 days (57$\pm$ 46 days). A significant congruence between MR Plaque imaging and histopathology was noted for IPH (sensitivity- 91%, specificity- 86%, k=0.774, p=<0.001), LRNC (sensitivity- 92.1%, specificity- 85.7%, k=0.697, p=<0.001), and ulceration (sensitivity- 84.6%, specificity- 78.1%, k=0.563, p=<0.001). The overall sensitivity and specificity in discriminating high risk plaque characteristics with MRimaging was 92.3% and 84.2% respectively (k- 0.77, p-<0.001).

Conclusion: The MR plaque imaging is capable of identifying the unstable plaque characteristics with high accuracy. This may have implication in selection of patients for carotid revascularization in asymptomatic carotid stenosis.

INTRODUCTION

INTRODUCTION

Stroke is the leading cause of death and long-term disability. Of the strokes, 80% are ischemic in origin. Identifying the etiological ischemic stroke subtype has implication in stroke recurrence and short and long-term outcome (1,2,3). Of the ischemic strokes, 20-40% of the strokes are due to large artery atherosclerosis, of which carotid disease is an important cause. (1,2,3). One of the important mechanisms of stroke is carotid artery plaque rupture and embolism (4). Carotid stenosis of ≥ 50% with history of stroke or transient ischemic attacks (TIA) benefit from carotid revascularization, both carotid endarterectomy (CEA) or stenting. In-addition to degree of stenosis, identifying the high-risk plaque is important in deciding the need of carotid intervention and in assessing the periprocedural risk (5). Conventionally, the risk of thromboembolism is assessed by the degree of carotid artery stenosis. Nevertheless, significance of plaque morphology as an additional factor for vulnerability is well-accepted currently (6,7,8,9). In patients with symptomatic moderate stenosis, the presence of high-risk plaque can be used in the decision making for revascularization. In asymptomatic carotid stenosis also, the high-risk plaque features may be used in the decision making for carotid revascularization (10,11,12,13). MR plaque imaging is the most accurate method to image the morphology of the plaque and differentiate intraplaque haemorrhage, large lipid core and thin fibrous cap. These features are suggestive of unstable plaque (14,15,16,17,18). MR plaque imaging has been found to have a good correlation with histopathology in identifying the high-risk group (19). So, the carotid plaque morphology will have implications in deciding on carotid revascularization in asymptomatic carotid stenosis and moderate symptomatic stenosis. In patients with high grade stenosis, identifying the high-risk plaque will help in predicting the periprocedural stroke risk. The American Heart Association has developed a classification for atherosclerotic plaque morphology dividing it into Types 1 through 6. This classification will

differentiate the stable and unstable plaques and can be correlated with MR plaque imaging. (20)

It is important to note that these diagnostic accuracy measures can vary between studies, and the performance of MR carotid plaque imaging may be influenced by several factors, including the field strength of the MRI scanner, pulse sequences utilized, image acquisition protocols, and the experience of the interpreting radiologist. Additionally, the accuracy of MRI may be influenced by factors such as the size and location of the plaque, the presence of ulceration or intraplaque haemorrhage, and the timing of imaging relative to symptoms.

In conclusion, MR carotid plaque imaging shows promise in assessing plaque composition and identifying high-risk plaques in patients with symptomatic carotid artery stenosis. While it is a valuable non-invasive imaging tool, it is important to consider the limitations and potential sources of variability when interpreting the results. Further research and technological advancements are continuously improving the accuracy and utility of MR carotid plaque imaging in clinical practice.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1.To evaluate the diagnostic accuracy of MR carotid plaque imaging in identifying the high-risk carotid plaque in symptomatic carotid stenosis and correlate with histopathology.

2.To correlate MR carotid plaque imaging features with clinical characteristics.

REVIEW OF LITERATURE

INTRODUCTION

According to the Global Burden of Disease study, there were 101 million prevalent cases of stroke, 12 million incident cases, and 655 million stroke-related deaths. Stroke is the second-leading cause of death and the third-leading cause of death and disability combined and globally in 2019. From 1990 to 2019, the total number of stroke incidents increased by 70%, the number of stroke deaths increased by 43% and the number of disability-adjusted life years (DALYs) attributable to stroke increased by 32% (21). According to estimates from the GBD research, low- and middle-income countries (LMICs) accounted for more than 85% of the world's burden of stroke. Over the past 20 years, India has undergone a substantial demographic, economic, and epidemiological transition. These have led to an increase in life expectancy and, as a result, a rise in the population of older people. In the past 20 years, the stroke prevalence in different parts of India has ranged from 44.29 to 559/100,000 and the cumulative incidence of stroke has varied from 105 to 152/100,000 people annually (22).

The mean age (58.3±14.7 years) and proportion of women (33%) were much lower than those of the populations of the West and China. Common risk factors included hypertension (60.8%), diabetes (35.7%), and tobacco use (32.2%). Large-artery (29.9%), cardiac (24.9%), small-artery (14.2%), other definite (3.4%), and undetermined (27.6%) were the stroke mechanisms (1).

Large vessel atherosclerosis is an important cause of stroke, with extracranial internal carotid artery stenosis significantly more common intracranial atherosclerotic disease (23). Ischemic strokes and transient ischemic attacks (TIAs) are frequently caused by embolism from, or low flow distally from an atherothrombotic plaque or thrombosis at the site of plaque rupture (24). Importantly, timely revascularization with carotid endarterectomy results in a considerable reduction in the incidence of recurrent stroke for patients with stroke or TIA caused by severe (> 50%) extracranial internal carotid artery (ICA) stenosis (7, 25).

Carotid endarterectomy (CEA) is currently recommended for patients with symptomatic carotid stenosis (50%) in hospitals with perioperative morbidity and mortality rates under 6%. This is based on the three landmark trials (The North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST), and Veteran Affairs Trial 309) (26-28). In clinical practice, surgical risk depends on the type of patients operated on, the technique used, and the skill of the operating team and most importantly the plaque characteristics. Several studies have also suggested the importance of plaque characteristics, rather than stenosis, about the future risk for stroke (29).

Additionally, the composition of the atherosclerotic plaque in individuals undergoing CEA is an independent predictor of periprocedural cardiovascular events. Approximately 5% and 9% of those over 65 are estimated to have asymptomatic moderate to severe (>50%) carotid stenosis, with a significantly higher frequency in men than in women (30,31). In the two largest studies showing a benefit for CEA in asymptomatic patients, the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the European Asymptomatic Carotid Surgery Trial (ACST), the overall incidence of ipsilateral ischemic events in medically treated patients was 2% per year (32,33). The number of asymptomatic subjects requiring CEA to prevent one ipsilateral disabling stroke annually is about 170. Therefore, a need to identify subgroups that have a high risk of ipsilateral ischemic stroke under medical treatment to make CEA cost-effective. There is growing evidence that, in addition to the severity of the stenosis, the composition of the carotid plaque may be an independent risk factor for ischemic stroke. Non-invasive imaging approaches can be utilised to assess the structure of carotid plaques in vivo. Several observational studies have revealed that increased plaque echolucency (a sign of plaque lipid and haemorrhage content) on ultrasonography is related with an increased risk of stroke or TIA distal to a carotid stenosis. As a result, research is being conducted to develop screening techniques that better determine the risk-benefit ratio for individuals undergoing surgical intervention. The potential role of vessel wall MR imaging, particularly 3T MR scanners, in

determining the risk of thromboembolic strokes from carotid disease is being researched extensively. Implementing high-resolution magnetic resonance imaging MR plaque imaging appears to be one of the most promising ways for more precisely determining the degree of stenosis and plaque features. In terms of sensitivity and specificity, this study investigated the agreement between 3 Tesla carotid MR imaging and histology for specific carotid plaque characteristics associated with vulnerability.

CAROTID PLAQUE COMPOSITION

A report from the Committee on Vascular Lesions of the Council on Atherosclerosis, American Heart Association (AHA), published in 1995, provided the classification of carotid lesions based on histological composition and structure, as well as how it reflects the temporal natural history of disease. The lesions were categorised using Roman numerals that represent a typical pattern of lesion progression, ranging from type I (initial lesions) to type VIII (fibrotic plaque) (34). Different plaques have varying proportions of various components (connective tissue extracellular matrix; crystalline cholesterol, cholesteryl esters, phospholipids; and cells such as monocyte-derived macrophages, T lymphocytes, and smooth muscle cells), resulting in a spectrum of lesions. Ulceration, hematoma, and thrombotic deposits worsen the condition, cause it to thicken and distort, and accelerate the transition from a clinically quiet to an overt disease (35,36).

The three main features of vulnerable plaque include Intraplaque hemorrhage, lipid necrotic core, and thin or ruptured fibrous cap. In addition, neoangiogenesis and dense plaque macrophage infiltration were highly linked with both histological cap rupture and time since stroke, implying probable causative relationships between plaque inflammation and plaque instability (37).

Terms for Atherosclerotic Lesions in AHA Histological Classification		
Type I lesion	Isolated deposition of macrophages & foam cells	Asymptomatic
Type IIa lesion	Fatty streak lesion w/ mainly intracellular lipid accumulation	Asymptomatic
IIb	Progression-resistant type II	Asymptomatic
Type III lesion	Intermediate lesion (preatheroma)- Deposition of intracellular lipids with in the plaque.	Asymptomatic
Type IV lesion	Atheroma Dense accumulation of extracellular lipid (i.e., lipid core). Inflammatory cell infiltration. No fibrous tissue formation, no surface defects or thrombosis.	Possibly symptomatic
Type V lesion	Fibroatheroma - Fibrous cap overlying necrotic lipid core. Inflammation w/in plaque & in the vasa vasorum of the artery wall. Prone to hematoma, thrombus formation, & fissuring	Possibly symptomatic
Type VI lesion	Fissuring & ulceration of plaque. Necrotic lipid core. Intraplaque hemorrhage & thrombus. Inflammation within the plaque	Probably symptomatic
Type VII lesion	Calcific lesion	Possibly symptomatic
Type VIII lesion	Fibrotic lesion	Possibly symptomatic

Table 1:AHA classification of Atherosclerotic Lesions in Pathology

HISTOPATHOLOGICAL CLASSIFICATION OF ATHEROSCLEROTIC PLAQUE

The American Heart Association has put forth a classification(Table 1& 2) for the atherosclerotic plaque morphology (38).

Terms for Atherosclerotic Lesions in Histological Classification		Other Terms for the Same Lesions Often Based on Appearance With the Unaided Eye	
Type I lesion	Initial lesion		Early lesions
Type IIa lesion	Progression-prone type II lesion	Fatty dot or streak	
IIb	Progression-resistant type II		
Type III lesion	Intermediate lesion (preatheroma)		
Type IV lesion	Atheroma	Atheromatous plaque,	
Type Va lesion	Fibroatheroma (type V lesion)	fibrolipid plaque,	
		fibrous plaque, plaque	
Vb	Calcific lesion (type VII lesion)	Calcified plaque	Advanced lesions,
Vc	Fibrotic lesion (type VIII lesion)	Fibrous plaque	raised lesions
Type VI lesion	A lesion with surface defect, and/or hematoma-haemorrhage, and/or thrombotic deposit	A complicated lesion, complicated plaque	

Table 2:Terms Used to Designate Different Types of Atherosclerotic Lesions in Pathology

CAROTID ARTERY STENOSIS

The NASCET criteria are used to calculate percentage diameter carotid stenosis. (Figure 1) Carotid stenosis was formerly thought to be underestimated using MR angiography techniques; however, with the introduction of high-resolution sequences and black blood techniques, no significant difference in stenosis assessment was shown with CT angiography (39). A percentage diameter stenosis of 70% to 99% was considered severe by NASCET standards. When the percentage diameter stenosis was 50%-69%, it was classified as moderate, while less than 50% was considered mild (26).

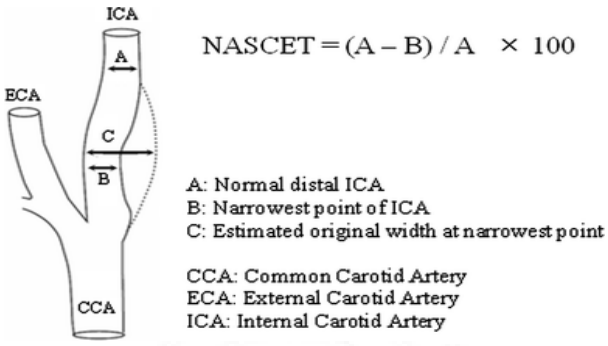

Figure 1: Diagram showing NASCET measurement for carotid stenosis.

Another method (Figure 2) based on ECST measurement is calculated as percentage diameter stenosis on the best angiographic view of the point of maximum narrowing, using an estimate of the original width of the artery at this narrowest point as the denominator and taking into account the slight widening of the normal ICA origin, which is where the majority of the stenoses were found (27).

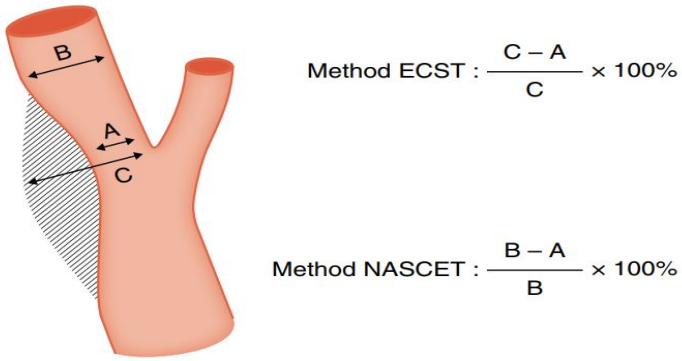

Figure 2: Diagram showing ECST vs NASCET measurement for carotid stenosis.

IMAGING MODALITY FOR ASSESSMENT OF VULNERABILITY OF PLAQUE

B-mode ultrasound is typically performed with a 4- to 7-MHz linear array transducer. To maximise visualisation of the atherosclerotic plaque, images are often acquired in longitudinal sections. Doppler colour and power can be utilised to further define the plaque boundary. B-mode carotid ultrasonography has great specificity but relatively modest sensitivity in detecting plaque surface ulceration. The lack of consistent inter and intraobserver agreement, as well as

a low signal-to-noise ratio, is one of the constraints of B-mode characterisation of carotid plaques. Ultrasonography has lower sensitivity for detecting plaque ulceration than CT, MRI, and histological tests, and it is especially poor for patients with moderate stenosis. Contrast-enhanced ultrasonography (CEUS) is used primarily to identify neovascularization within carotid plaques. The intravenous microbubble contrast agent used in CEUS helps to discriminate between total carotid occlusion and high-grade stenosis, as well as to detect plaque ulceration and neovascularisation. Enhancement within plaque indicate plaque vulnerability (40).

Multidetector CT (MDCT) and dual-source CT (DSCT) are the two main CT techniques for plaque characterization. A technique called bolus tracking CT angiography (CTA) is used to scan plaques. On the basis of voxel Hounsfield units (HUs), MDCT can be used to characterise plaque calcification, fibrous plaque thickness, IPH, and LRNCs. Calcifications are easily distinguished by their high density (mean 250 HU). However, the CT densities of LRNC, connective tissue, and IPH (approximate means 30, 45, and 100 HU) overlap significantly.

CT has several drawbacks, including beam hardening artefact from heavily calcified plaques, the necessity for iodinated contrast, and radiation exposure (41). Studies have been done comparing the results of histological examination with FDG-PET/CT scans. Masteling et al. discovered that locations with macrophage infiltration were where there was strong FDG activity in carotid plaques. Although FDG uptake is substantially linked to inflammation, plaque neovascularization is only marginally associated with FDG uptake. Therefore, this imaging modality might not be the best option to evaluate the plaque vulnerability (42).

MR PLAQUE IMAGING

Currently MR plaque imaging is the gold standard modality for in vivo carotid plaque morphology assessment. It is able to delineate multiple vulnerable features of plaque such as intraplaque haemorrhage, lipid rich necrotic core and ulceration. Both 1.5T and 3T MRI may

be used although later is considered better because of superior spatial resolution and signal to noise ratio (SNR). Clinical 7T MRI for evaluating plaque characteristics is currently being developed. Compared to other imaging methods, carotid MRI offers a number of benefits. Although ultrasonography is a widely used screening tool, its spatial and contrast resolution are constrained, which lowers its accuracy when comparing carotid stenosis and plaque components to MRI and in patients with short necks, a precise examination is also challenging (40). Although computed tomography (CT) has a high spatial resolution, MR offers a higher contrast resolution. Additionally, it uses ionising radiation and imaging strongly calcified lesions can exaggerate the severity of the condition. Positron emission tomography (PET) is useful for characterising the inflammation of a plaque but is insufficient for accurately depicting other plaque characteristics and the degree of stenosis (41). Only two-dimensional planes can be accurately shown by digital subtraction angiography, which is invasive, exposes the patient to radiation, and has other procedural hazards. Therefore, MRI is the most precise and adaptable non-invasive clinical imaging modality currently in use.

High-resolution vascular imaging necessitates the use of specific surface coils and high field MR devices. Studies comparing T1-, T2-, and proton density-weighted black-blood techniques at 1.5- and 3-T have found that employing the higher field strength system significantly improves signal to noise (SNR), contrast-to-noise ratios, and overall picture quality (43). We can further improve image quality by boosting SNR and using dedicated surface coils (44, 45).

MRI TECHNIQUE

MR protocol used for plaque imaging varies between the institutions. For plaque imaging, several institutes now frequently use 3D sequences. Sequences in 3D TOF, 3D MPRAGE, and 3D fast spin echo (FSE). Time-of-flight (TOF), precontrast, and postcontrast MR angiography (MRA) procedures are bright-blood sequences that enable the identification of plaque ulcerations and IPH. The highly T1-weighted magnetization-prepared rapid acquisition

gradient echo (MPRAGE) sequence is particularly helpful because it can more accurately detect IPH by decreasing signal from LRNCs and fibrous tissue (46,47). The imaging algorithm that's followed is adapted from the study by Hingwala et al (47) (Fig.3). The same algorithm was used by Cai et al and Saam et al in their studies (48,49).

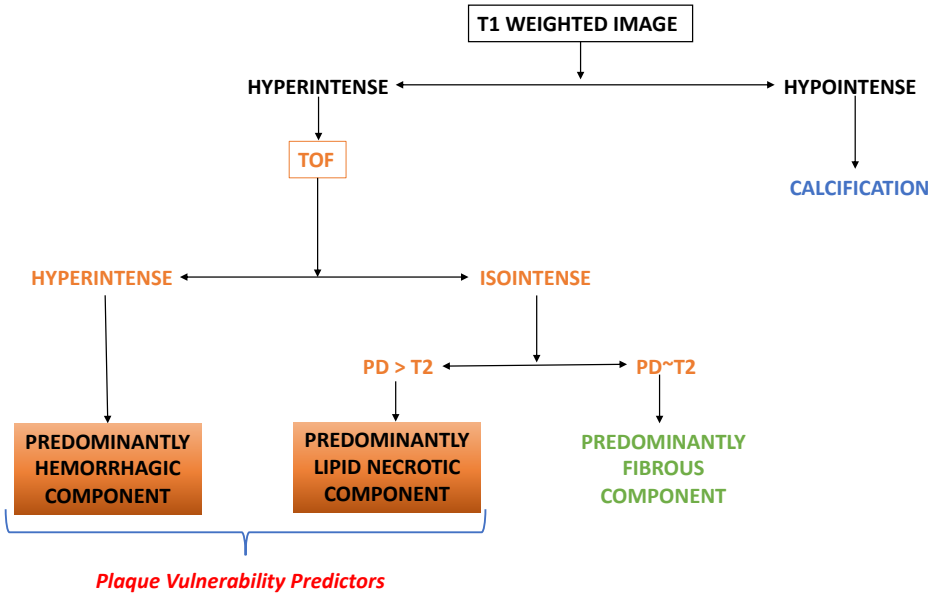

Fig. 3: Algorithm for detecting carotid plaque composition based on MR signals in various sequences. Adapted from study by Hingwala et al (47).

The process of development of atherosclerotic plaques in blood vessels, initiates with an outward expansion of the vessel wall, which can be observed on pathological specimens. Subsequently, MRI enables the visualization of the artery's compensatory dilation and eccentric remodelling, even before additional plaque deposition leads to narrowing of the vessel's lumen. By adjusting the image acquisition parameters, MRI can effectively identify plaque components such as the presence or absence of a lipid core, fibrous cap, fibrous tissue components, and calcification. These capabilities provide valuable insights into plaque characteristics and vulnerability, aiding in the early assessment and management of patients at risk of cardiovascular events (50).

LIPID NECROTIC CORE

The LRNCs (lipid-rich necrotic cores) usually present as distinct signal changes found eccentrically along the arterial lumen. On T1-weighted images (T1WI), the lipid material appears mildly hyperintense, and on MPRAGE (magnetization-prepared rapid acquisition gradient echo) images, it lacks signal. Additionally, the plaques are isointense on TOF (time-of-flight) images and hypo- to iso-intense on T2-weighted images (T2WI). One of the key characteristics of LRNCs is their avascular nature, which means they do not enhance after the administration of contrast. As a result, they exhibit a characteristic low signal on post-contrast T1WI, which can help distinguish them from the surrounding enhancing fibrous cap (51).

INTRA PLAQUE HEMORRHAGE

IPH (Intraplaque haemorrhage) occurs within a LRNC, leading to its presence being superimposed on the lipid material during imaging. On the other hand, thrombosis results from the extension of a focal defect in the overlying fibrous cap, causing irregularity in the vessel lumen. Some researchers have speculated that this irregularity might be due to the rupture of plaque neovascularity (52).

Imaging findings related to IPH are categorized based on their chronicity:

1. **Fresh IPH (<1 week)** tends to appear bright on T1-weighted images (T1WI) and iso- to hypointense on T2-weighted images (T2WI) and proton density (PD) images.
2. **Recent hemorrhage (1–6 weeks)** appears hyperintense on T1WI, T2WI, and PD images.
3. **Old hemorrhage (>6 weeks)** appears dark on corresponding sequences.

TOF (time-of-flight) images can also be employed to differentiate IPH from LRNC. LRNC appears isointense on TOF images, while fresh and recent IPH appears hyperintense

FIBROUS CAP

The fibrous cap, when thick and intact, can be easily identified as a uniformly hypointense band between the vessel lumen and LRNC (lipid-rich necrotic core), and it typically shows enhancement on post-contrast images. If the fibrous cap is thin but still intact, it may appear absent on TOF (time-of-flight) and contrast-enhanced T1-weighted (CE-T1W) images, with a smooth luminal surface. However, when the fibrous cap is ruptured, it may either become invisible or exhibit disruption, leading to irregularity of the luminal surface.

High-resolution research coils can greatly aid in visualizing these MRI findings, and there is a strong agreement (89%) between such MRI observations and histological findings. Consequently, imaging evidence of fibrous cap rupture is highly specific. While ulcerations can be detected on both contrast-enhanced magnetic resonance angiography (CE-MRA) and TOF images, CE-MRA has been found to be superior in this regard. (47,53,54).

PLAQUE CALCIFICATION

On magnetic resonance imaging (MRI), calcifications are visualized as hypointense structures on various sequences, including T1-weighted (T1), T2-weighted (T2), proton density (PD), and time-of-flight (TOF) imaging. The calcific material appears jet black, maintaining its hypo intensity even on black-blood sequences. Susceptibility-weighted images typically show blooming signal around the calcifications. Similar to LRNCs, calcifications also tend to be located eccentrically along the luminal surface of the vessel. According to a study by Saam et al., the sensitivity and specificity of detecting calcifications on MR were reported to be 76% and 86%, respectively. For larger lesions (>2 mm2), these values increased to 84% sensitivity and 91% specificity. Additionally, Puppini et al. reported the sensitivity and specificity of characterizing calcifications to be 80% and 94%, respectively (55, 56, 57).

ROLE OF DIFFUSION SEQUENCE AND SUSCEPTIBILITY IMAGING

To address the need for non-contrast evaluation of plaque characteristics, researchers explored the use of Diffusion-Weighted Imaging (DWI), especially in detecting the lipid necrotic core. Early studies utilized conventional spin-echo DWI sequences primarily in the analysis of ex vivo plaque specimens from the carotid artery. In one study, Clarke et al. conducted a multi-sequence examination that included DWI, leading to the conclusion that incorporating a DWI sequence improved the ability of supervised classification algorithms to identify different plaque components (58).

In another study conducted in 2007, Qiao et al. conducted a similar investigation and generated apparent diffusion coefficient (ADC) maps. They reported the range of ADC values in both lipid necrotic core and fibrous cap tissue (59). These studies aimed to explore the potential of DWI in characterizing plaque components without the need for contrast agents.

Raman et al. conducted an in vivo evaluation of carotid plaques and observed a reduction of T2* in plaques associated with symptoms. This reduction was believed to be due to higher levels of T2*-shortening forms of iron. In cases of acute stroke, susceptibility-weighted imaging has been utilized to demonstrate intra-arterial thrombus (60). This imaging technique has also been applied in assessing calcification in the femoral artery using a 3D acquisition protocol with high vessel wall contrast and broad coverage (61). Additionally, susceptibility imaging is sensitive to small amounts of blood components, such as hemosiderin, potentially enabling the study of both calcifications and haemorrhage in the future. Currently, the evaluation of carotid intraplaque haemorrhage (IPH) primarily relies on magnetic resonance imaging (MRI) techniques, including time-of-flight (TOF), magnetization-prepared rapid acquisition with gradient echo (MP-RAGE), and T1-weighted sampling perfection with application of optimized contrasts using different flip angle evolution (T1-SPACE) sequences. The signal intensity of IPH on MRI depends on the integrity of erythrocytes and the oxidation

state of haemoglobin (62). Haemoglobin undergoes degradation from deoxyhaemoglobin to methaemoglobin in the acute stage and later to hemosiderin in the chronic stage. MP-RAGE has demonstrated high accuracy in detecting carotid IPH, as validated by histology (63). However, a previous study indicated that the sensitivity of MP-RAGE decreased when detecting IPH with a small size or when coexisting with calcification (64). In recent research, the QSM (Quantitative Susceptibility Mapping) sequence has been evaluated for differentiating haemorrhage from calcification in carotid plaque (65).

MANAGEMENT OF CAROTID STENOSIS

Management of patients diagnosed with carotid stenosis is mainly decided based on symptoms and degree of stenosis currently. Evidence-based management is followed as per the ESC 2017 guidelines briefly summarised in Fig.4 (66). Best medical therapy involves the use of antiplatelet agents and statins generally in addition to other risk factor modification. Lifestyle modifications: Adopting a healthy lifestyle can help manage carotid stenosis and reduce the risk of stroke. This includes quitting smoking is crucial as smoking contributes to the progression of carotid artery disease. Following a diet low in saturated fats, cholesterol, and sodium can help manage cardiovascular risk factors. Engaging in regular physical activity improves cardiovascular health and reduces the risk of stroke. Maintaining a healthy weight helps control blood pressure, cholesterol levels, and overall cardiovascular health. Managing hypertension and high cholesterol levels is important in preventing the progression of carotid stenosis. This may involve lifestyle changes, such as diet and exercise, as well as medication prescribed by a healthcare professional.

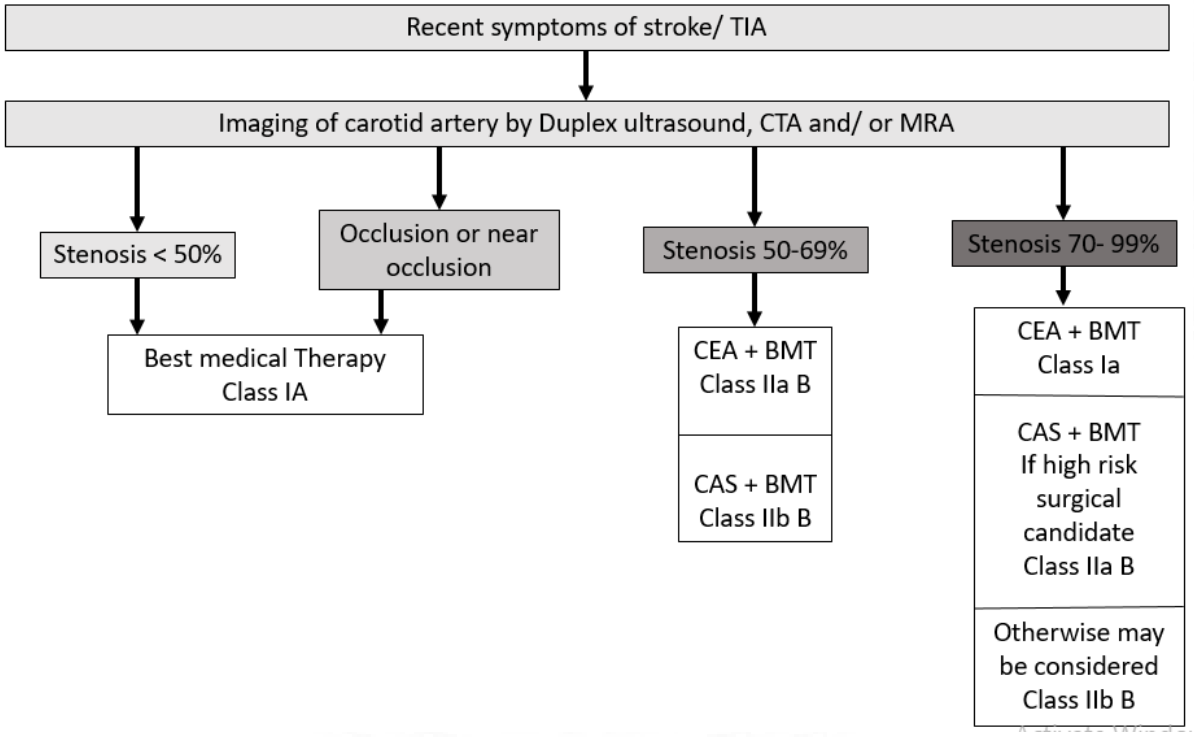

Fig.4: Flow chart showing the evidence based management options in carotid artery stenosis

Antiplatelet therapy

The Clopidogrel and Aspirin Regimen for the Reduction of Emboli in the Symptomatic Carotid Stenosis Trial was designed to evaluate the efficacy of dual antiplatelet therapy with clopidogrel and aspirin, compared with aspirin alone, on asymptomatic embolization in patients with recently symptomatic stenosis(67). Patients were screened with transcranial Doppler and if micro-embolic signals (MES) were detected, they were randomized to clopidogrel and aspirin or aspirin alone. 110 out of the 230 subjects showed micro embolic signals of which 107 were randomized. The analysis showed a significant reduction in the primary endpoint with 43.8% patients on dual antiplatelet therapy were MES positive on day 7, compared with 72.7% of subjects in the aspirin-alone group (relative risk reduction, 39.8%). During the 1-week follow-up, there was a high rate of recurrent ipsilateral events in the monotherapy group, with a 7.1% risk of stroke and a 12.5% risk of recurrent TIA. Forty-four percent of patients still had MES on the seventh day even in the dual therapy group. Thus, complementary approaches that target other processes, like inflammation may be beneficial.

Statins

A relationship between low-density lipoprotein-cholesterol (LDL-C) reduction by statins and carotid artery IMT has been demonstrated(68). Statins reduce the lipid content within the plaque and hence stabilize the plaque from disruption and inflammatory processes. Its action on the inflammatory process is due to the inhibition of various surface receptors' inflammatory cells. The effect of 3 months of the pravastatin on the composition of human carotid plaques removed during carotid endarterectomy for symptomatic severe stenosis has been evaluated(69). Reduction of lipid, oxidation, MMP2, and apoptosis were all effects of pravastatin.

CAROTID STENTING

There is currently insufficient evidence to support a widespread change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for carotid artery stenosis. However carotid stenting is generally advised in patients with significant coronary heart disease, prior radiation to the neck, high carotid bifurcation, etc. where surgery may be difficult.

THE UNMET NEED IN CAROTID PLAQUE IMAGING

Accurate imaging and characterization of carotid plaques are crucial for identifying individuals at risk of stroke or other cardiovascular events and guiding appropriate treatment decisions. Current imaging techniques provide limited information on plaque composition and vulnerability. It is essential to accurately identify high-risk plaques that are prone to rupture and cause strokes. This requires the development of imaging methods that can differentiate between stable and unstable plaques, assess inflammation levels, and determine the presence of features associated with vulnerability, such as intraplaque haemorrhage or fibrous cap thinning. There is a need for more objective and standardized methods to quantify plaque burden and characterize plaque features. This could involve the development of automated algorithms or software tools that can provide quantitative measurements of plaque volume, degree of stenosis (narrowing), and other relevant parameters. This would enable better tracking of disease progression and response to treatment over time. Although ultrasound is commonly used for carotid plaque imaging, it has limitations in visualizing deep or heavily calcified plaques accurately. Non-invasive imaging techniques that can overcome these limitations and provide detailed information about plaque morphology and composition are needed. This could involve the advancement of imaging modalities such as MRI or CT with improved spatial resolution, contrast, and sensitivity to specific plaque features. Understanding the biological processes occurring within carotid plaques is crucial for developing targeted therapies and assessing treatment efficacy. Current imaging techniques primarily provide anatomical information but lack the ability to visualize plaque biology in vivo, such as inflammation, angiogenesis, or cellular activity. Novel imaging approaches that can provide molecular or functional information about plaque biology are needed to advance our understanding and management of carotid artery disease. Carotid plaque imaging is often performed at discrete time points, but there is a need for continuous or longitudinal monitoring of plaque progression and regression. Long-term studies involving repeated imaging

assessments would provide valuable insights into the natural history of carotid plaques and their response to interventions.

Addressing these unmet needs in carotid plaque imaging would contribute to better risk stratification, treatment decision-making, and monitoring of patients with carotid artery disease. Continued research and technological advancements in this field are essential to improve patient outcomes and reduce the burden of stroke and cardiovascular disease.

MATERIALS AND METHODS

Study Population:

This was a prospective study carried out between November 2021 and December 2022 after receiving approval from the institutional ethical committee. All subjects who took part in this study provided written, informed consent. Following a multidisciplinary stroke team meeting, patients with moderate to severe (>50% stenosis) carotid artery stenosis who were scheduled for carotid endarterectomy were considered for inclusion. The decision regarding the need for carotid endarterectomy was as per the standard guidelines. The recruitment of patients was done by the principal investigator and co-principal investigators. All patients who were eligible were recruited for the study.

ELIGIBILITY:

Inclusion criteria:

1. Age more than 18 years
2. Symptomatic carotid artery stenosis (50-99% stenosis)
3. Patient who are willing to undergo MRI plaque imaging.
4. Patient who are planned for carotid endarterectomy.

Exclusion Criteria:

1.Asymptomatic carotid artery stenosis

2.Any contraindications for MRI Carotid Plaque Imaging

3.Renal dysfunction

NUMBER:

We estimated the sample size based on the following assumptions. Assuming proportion of high-risk plaques in the study population as 50%. Sensitivity of MR vessel imaging to predict high risk plaques = 95% with a margin of error of 10% and Specificity of MR vessel imaging to predict low risk plaques = 95% with a margin of error of 10%. Margin of error is to explain the possible variability in sensitivity and specificity.

The required sample size is 36 using the formula-

$n_{sensitivity} = Z^2$ x sensitivity (1-sensitivity)/d^2 (prevalence)

$n_{specificity} = Z^2$ x specificity (1-specificity)/d^2 (prevalence)

n=3.84*0.95*0.05/(0.01*0.5)= 0.1824/0.005 = 36.48

Where Z=1.96, Z^2 =3.84, sensitivity=0.95, d=0.10, prevalence=0.5,

For detecting 95% specificity with a margin of error of 10% also we need 36 patients. Hence the final sample size is rounded to be 40.

STUDY DESIGN

Consecutive patients who were planned for carotid endarterectomy following the detection of significant (>50 %) carotid artery stenosis identified with non-invasive imaging such as duplex sonography were included in the study. Each patient had a CT angiogram and/ or MRI study in addition to the ultrasound. Patient interviews were conducted to gather clinical information, which was further supplemented by reviewing the patients' medical charts According to the protocol listed below, eligible patients had magnetic resonance carotid plaque imaging. Magnetic resonance imaging data for the study was extracted from the Picture Archiving and Communication System (PACS), anonymised, and separated into numbered files. These images were analysed by a reader with 5 years of experience in interpreting diagnostic vascular imaging studies who was blinded to clinical data and other imaging tests. Prior to the evaluation, each MR image was given an image-quality grade from 1 to 4, with 1 denoting poor image quality and 4 denoting outstanding image quality. The analysis excluded studies with overall image quality ratings of 1 and 2. The images were independently analysed to evaluate specific parameters, including the signal intensities of the carotid plaque, which were compared relative to the signal in the sternocleidomastoid muscle on the same side as the carotid artery being examined. Various imaging sequences were used for this assessment, as outlined below. Subsequently, the patients underwent revascularization through carotid endarterectomy, and the carotid plaques were removed en bloc. A pathologist specialized in vascular disease reviewed the histopathology of the excised plaques. After data collection, statistical analysis was performed to draw conclusions and make inferences based on the findings.

FLOW CHART OF STUDY DESIGN

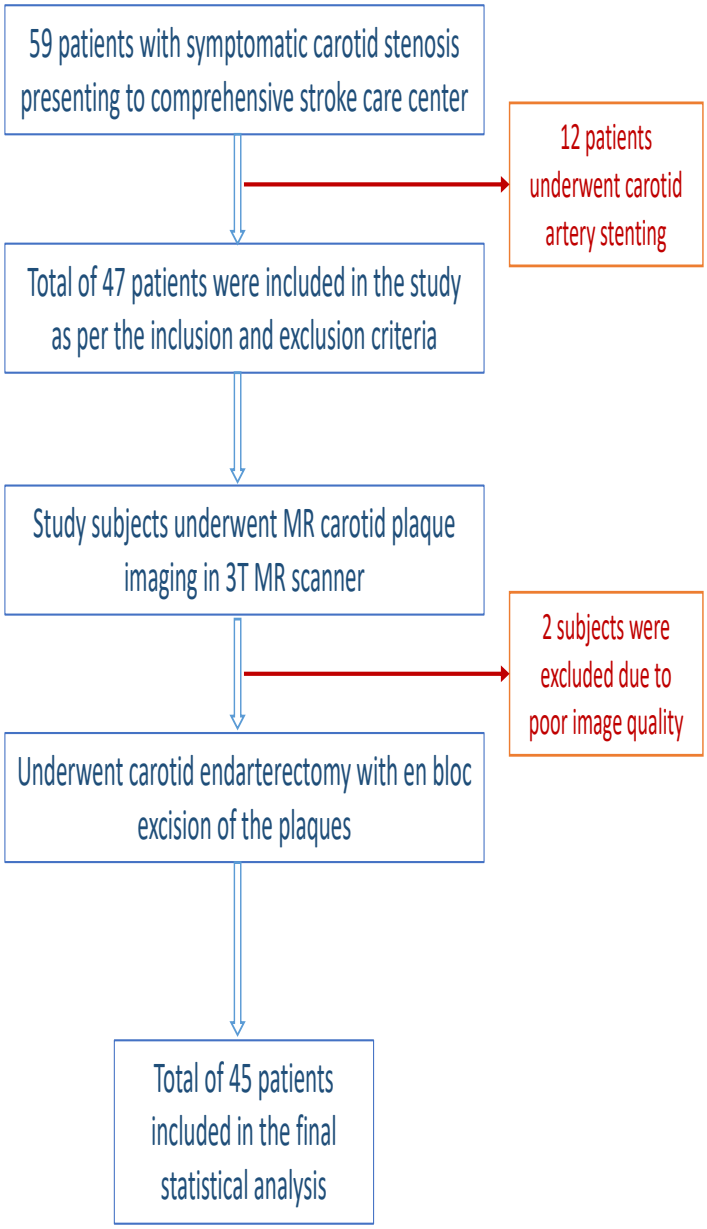

Fig. 5- Flow chart showing the study design

STUDY PROTOCOLS

CT acquisition and processing :

Philips CT scanner was used for the scans. Following the infusion of 60 ml of iodinated contrast media (Isovue 370, Bracco Imaging), the acquisition began utilising a bolus tracking method. The source data were then reconstructed into 1 mm axial, 7 mm axial, sagittal, and coronal maximum intensity projection (MIP) pictures, which were then transferred to a picture archiving and communication system (PACS) for inspection.

MRI PROTOCOL

The participants of the study underwent Carotid Plaque MR imaging using a General Electric Discovery 750E 3.0 Tesla machine equipped with a 6-channel carotid coil (Fig. 8). Before placing the patient in the MR scanner, ultrasonography was employed to mark the level of maximum carotid stenosis on the skin. This pre-scan marking ensured optimal positioning of the carotid surface coil, resulting in better signal quality (Fig. 7).

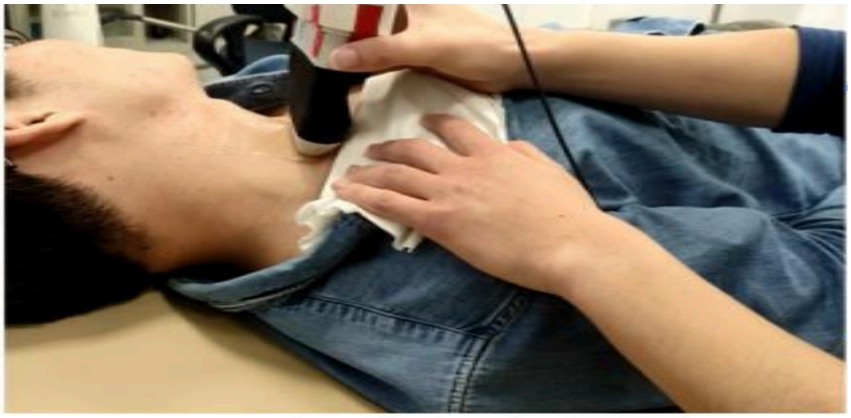

Fig.6: Technique of marking the site of carotid plaque using ultrasonography so as to ensure optimal positioning of the carotid coil

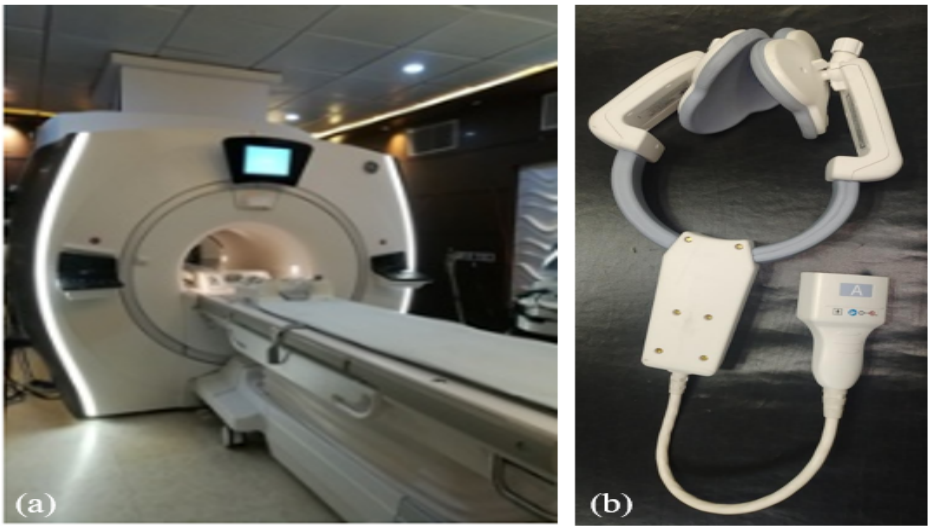

Fig. 7: (a) GE 3 Tesla Discovery scanner used for the study. (b) 6 channel carotid coil used for the study

A standardized carotid plaque protocol was followed to obtain images of the carotid vessel, which included the following sequences:

1. Three-dimensional (3D) time of flight (TOF) sequence (TR: 4.9, TE: 2.0).
2. Axial turbo spin echo (TSE) fast spin T1-weighted imaging (T1WI) (2 mm thick).
3. Axial TSE fast spin T2-weighted imaging (T2WI).
4. Axial TSE fast spin proton density-weighted imaging (PDWI).
5. Long-axial TSE fast spin T1WI (2 mm thick).
6. Dixon volumetric interpolated breath-hold examination (VIBE) sequence, including in phase, out of phase, fat image, and water image (TR: 15.2, TE: 4.9, matrix: 320 × 320, slice thickness: 0.76, flip angle (FA): 9, NEx: 1, echo: 1).
7. Contrast-enhanced magnetic resonance angiography (CE MRA) sequence (TR: 3, TE: 1.15, matrix: 512 × 80%, slice resolution: 60%, FA: 24, NEx: 1).
8. Post-contrast axial TSE fast spin T1WI.

Parameter	TOF	T1	T2	PD	DWI *b – 10/ 500*	T2FS	CUBE T1 FS
Acquisition Mode	3D	2D	2D	2D	2D	2D	3D
TE(ms)	6	15	90	12	71.5	90	11
TR(ms)	25	500	2000	4000	3800	2000	600
Echo-train length	-	4	12	5	-	12	20
Excitation flip angle(degrees)	20	125	111	90	-	111	-
No. of signals acquired(NEX)	1	2	4	2	2/6	4	2
FOV	15 x 15	12 x 12	12 x 12	12 x 12	8x 4	12 x 12	16 x 16
Matrix Size	320 x 224	320x192	256x192	256 x 192	120x60	256x192	192 x 192
No. of sections	34	15	15	15	11	15	116
Section thickness(mm)	1.2	2	2	2	4	2	0.7
Imaging time(min)	3.1	2.5	4.24	5.28	4.21	4.24	6.35
Pixel Sixe	0.6x0.9	0.4x0.6	0.5x 0.6	0.5 x 0.6	0.7x0.7	0.5x 0.6	0.8 X 0.8
Bandwidth	20.83	15.63	62.5	62.5	100	62.5	62.5

Table 3: MR Sequence parameters used as part of the study

All images were acquired in the transverse plane, except for the CUBE sequences, which were performed in the sagittal plane and cantered to include the carotid bifurcation on the affected side. The regions of carotid stenosis were identified using rapid-screening TOF MRA, which evaluated the middle 15 cm of the neck. The specific magnetic resonance imaging sequences used, along with their parameters, are summarized in Table 2.

In order to retain clinically acceptable acquisition times while ensuring robustness against spontaneous patient movements, a typical diffusion-weighted echo-planar sequence was used in this study. Additionally, T2, T2 FS, PD, and CUBE T1 sequences were processed using the zero interpolation technique (ZIP). The GE advantage workstation was utilised to

independently analyse the images, and GenIQ software was used for all evaluations, including the evaluation of diffusion parameters.

PLAQUE RESECTION:

Standard non-patch carotid endarterectomy procedures were carried out. Every effort was made during surgery to thoroughly resect the plaque in one piece. All patients are placed in the supine position, then the head is placed on a firm holder and the neck is extended and turned away from the side of operation (Fig. 9). In order to remove the entire plaque, a longitudinal incision has been made along the anterior margin of the sternocleidomastoid muscle (SCM). The plaque was transferred without manipulation into a formalin bottle, sealed, and sent for pathological evaluation.

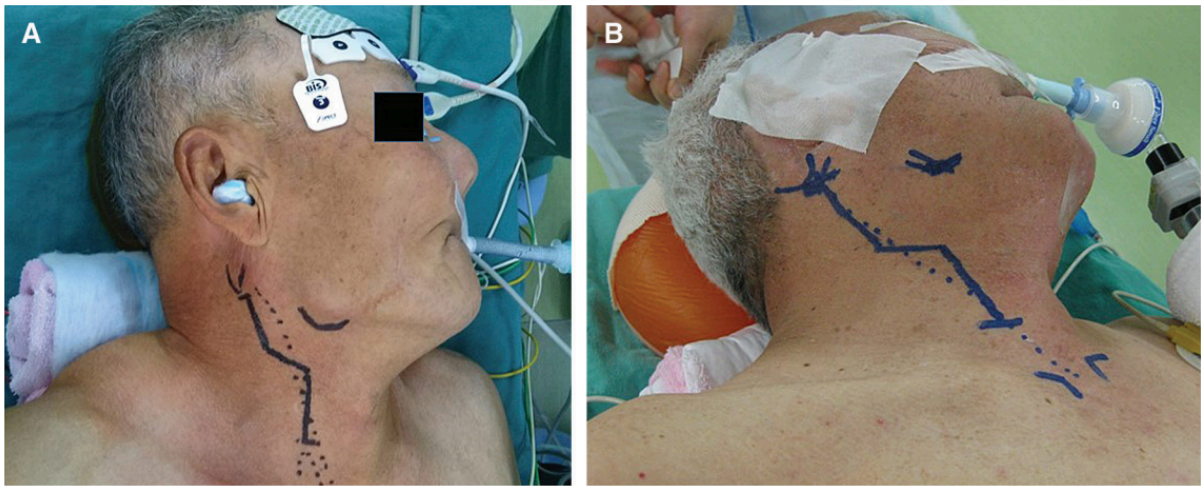

Fig. 8: A. Routine neck extension and head rotation (about 45°) to the opposite side. B. Longitudinal incision along the anterior margin of SCM.

HISTOPATHOLOGICAL ANALYSIS:

The histological analysis was carried out blinded to status of the patients and the results of the plaque analysis in MRI. Following surgery, the specimens were fixed in 10% neutral buffered formalin, serial cross-sections were taken at intervals of 2mm and the entire specimen was processed using standard procedure established in the pathology laboratory. On all specimens, the following stains were performed: Haematoxylin and Eosin (H & E), Masson's trichrome (MAT) and elastic van Gieson (EVG). All the slides were assessed by the pathologist (DN). The histological features were scored using a semi-quantitative method indicated in the Table below (70, 71). Based on the presence of lymphocytes and histiocytes on H & E sections, inflammation was evaluated. The atherosclerotic plaques were also classified as per the American Heart Association (AHA) histological classification of atherosclerosis (72). Thin cap was defined as minimum cap thickness of ≤200μm (2, 3). The cap thickness was measured on H & E sections using the Zeiss Axio Imager A2 microscope with Zen software (Carl Zeiss, Germany).

According to the Semi-quantitative assessment used, the majority of the plaques were classified as stable while the perhaps and certainly unstable plaques were classified as susceptible. Additionally, the sole signs of instability taken into consideration for analysis were the large lipid necrotic core, plaque ulceration, and intraplaque haemorrhage.

Histological parameter	Grade 1	Grade 2	Grade 3	Grade 4
Haemorrhage	Absent	Small	Large (> 2mm in length, >0.5mm in width)	-
Thrombus	Absent	Small	Large	-
Lipid core	Absent	Small	Large (at least 50% of plaque thickness)	-
Fibrous tissue	Little fibrous tissue	~50% fibrous tissue	>50% fibrous tissue	-
Foam cells	Absent	< 50 cells	≥ 50 cells	-
New vessels	Absent	< 10 per section	≥ 10 per section	-
Calcification	Absent	stippling	nodules	-
Plaque inflammation	Absent	Mild (occasional cells or 1 group of >50 cells)	Moderate (2-5 groups of >50 cells)	Dense (>5 groups of >50 cells)
Cap inflammation	Absent	< 10 cells	10-50 cells	> 50 cells
Cap status	Intact	Probably intact (artifactual break)	Probably ruptured (site of rupture not clear, but thrombus adherent to lipid in lumen)	Definitely ruptured
Overall instability	Definitely stable (predominantly fibrous, few inflammatory cells, intact cap)	Probably stable (one feature of instability: small haemorrhage or inflammation)	Probably unstable (features of instability, but no rupture: inflammation, thin cap, large lipid core)	Definitely unstable (rupture, thrombus, large haemorrhage, thin inflamed cap)

Table 4. Semi-quantitative scoring of various histological parameters

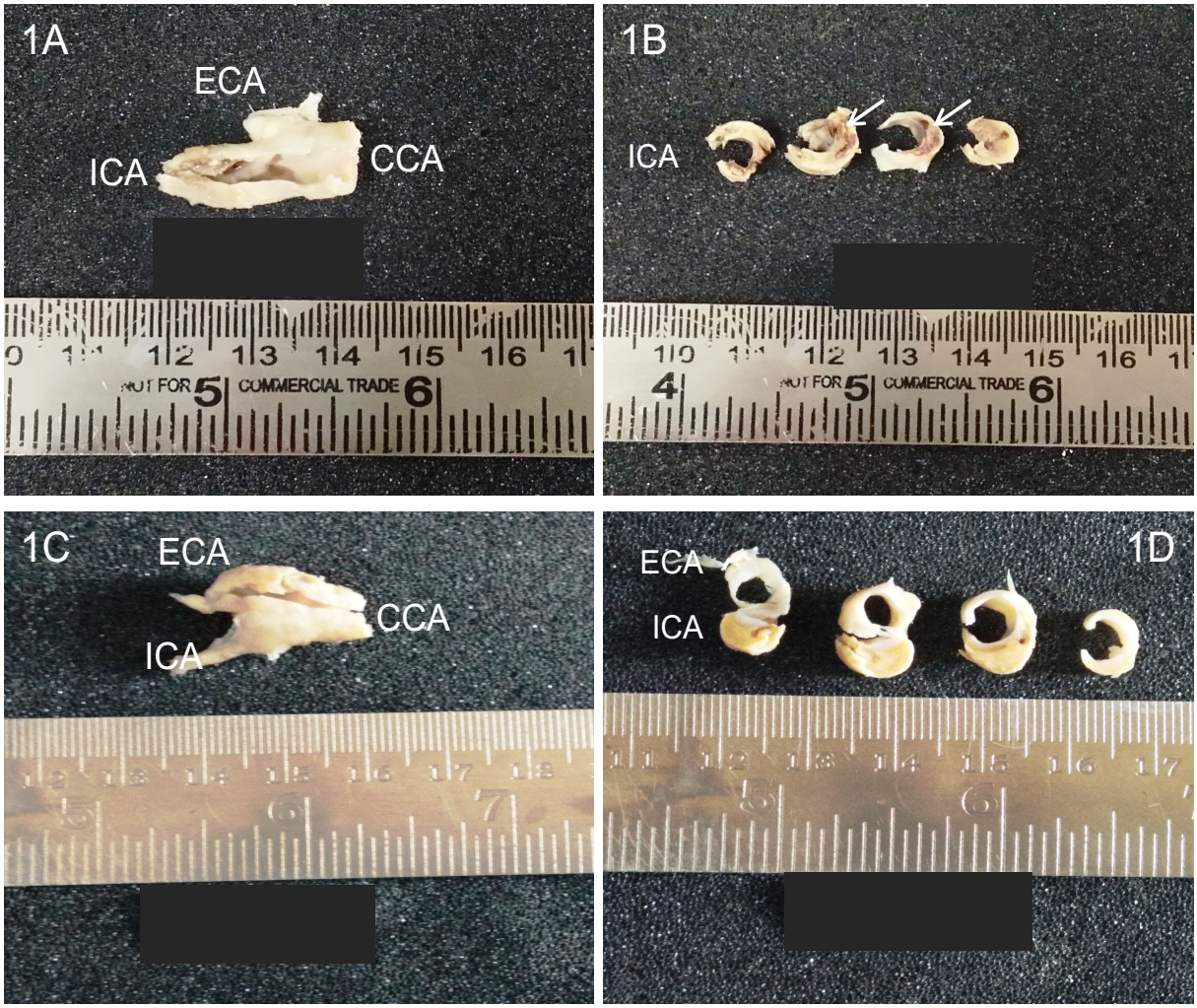

Figure 9. Gross appearance of endarterectomy specimens
Intact (1A, 1C) and serial cross-sections (1B, 1D). Brownish discoloration (arrows) indicating intraplaque haemorrhage.
ICA: internal carotid artery, ECA: external carotid artery

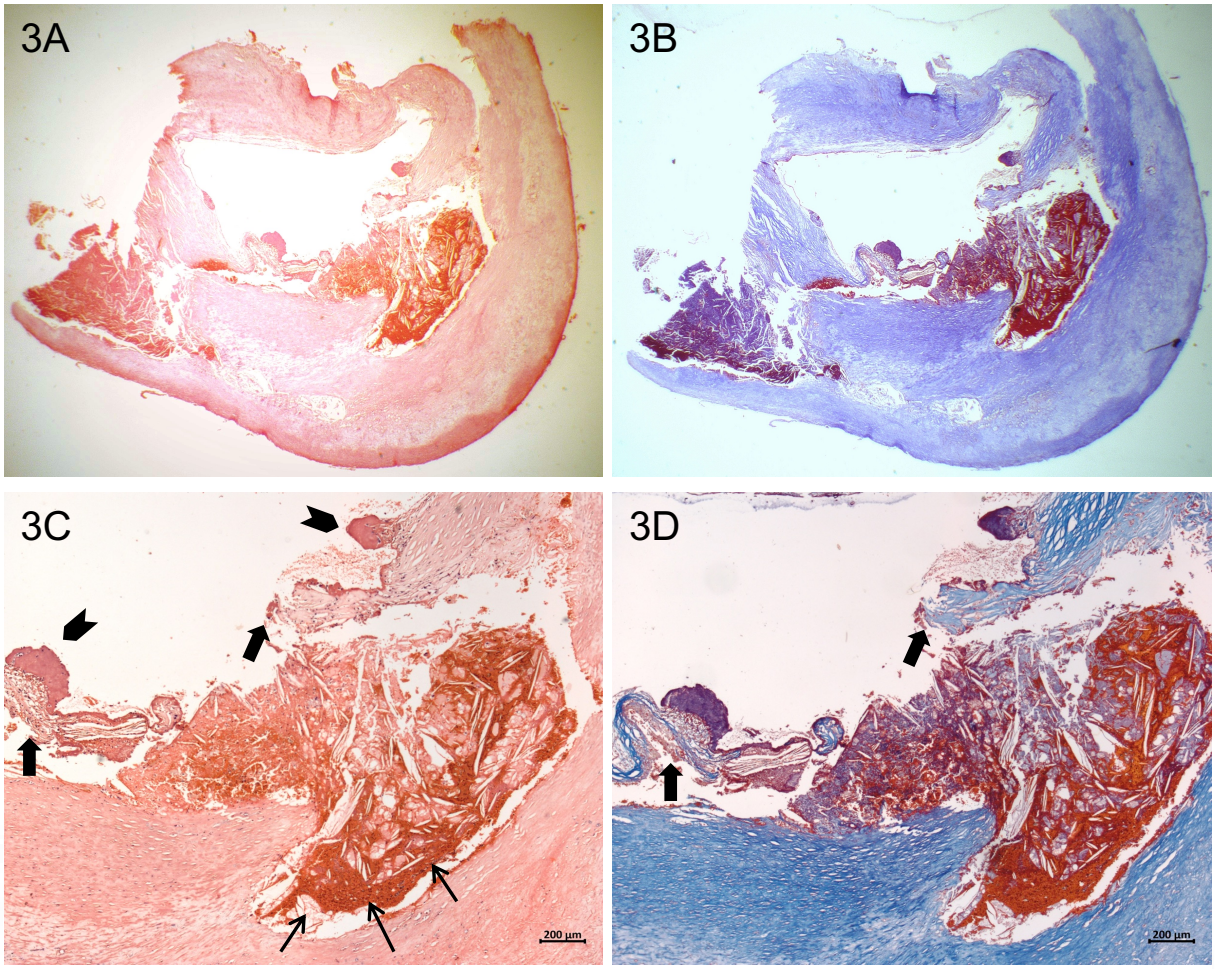

Figure 10. Intraplaque haemorrhage with ruptured cap
Several RBCs (3C, thin arrows) in lipid core admixed with cholesterol clefts and the two ends of the ruptured fibrous cap (3C & 3D, thick arrows) with adherent fibrin thrombus (3C, arrow heads).
[3A, 3C: Haematoxylin and Eosin, 3B, 3D: Masson's trichrome
3A-3B: Original magnification 16X,
3C-3D: Original magnification 50X, Scale bar 200µm]

STATISTICAL ANALYSIS

Continuous variables were presented as mean ± 1 standard deviation (SD) ranges. To evaluate the quantification of stenosis using MR and CT, the Pearson correlation test was conducted. The diagnostic accuracy, including sensitivity and specificity, were assessed, and the chi-squared test was used to compare nominal variables representing plaque components. A p-value of less than 0.001 was considered indicative of a significant difference. Diagnostic accuracy measures were calculated using the percentage of agreement and Cohen's kappa (κ) statistic. Kappa statistical analysis was done for the assessment of the correlation between MR vulnerability and histological vulnerability parameters. Kappa values were taken as <0 No agreement; 0 - 0.20 Slight agreement; 0.21 - 0.40 Fair agreement; 0.41- 0.60 Moderate agreement; 0.61 - 0.80 Substantial agreement and 0.81-1.0 Strong or Perfect agreement. Statistical analysis was performed using IBM SPSS 23 analysis software.

RESULTS

RESULTS

Due to movement artefacts on MRI, two patients were eliminated from the study, leaving 45 subjects for the final analyses.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The mean (± SD) age was 65.06 ± 7.7 years, with 77.8% of the subjects being over the age of 60. In the study population, the lowest age was 45 years and the maximum age was 84 years. Only seven (15.56%) of those being treated were female. The average time to CEA was 57 days (SD ± 46), although only 8 patients (17.7%) had surgery within two weeks.

Sex distribution

Table 5: Frequency distribution of sex in the study population

Sex	Frequency	Percent
Male	38	84.44
Female	7	15.56
Total	45	100.0

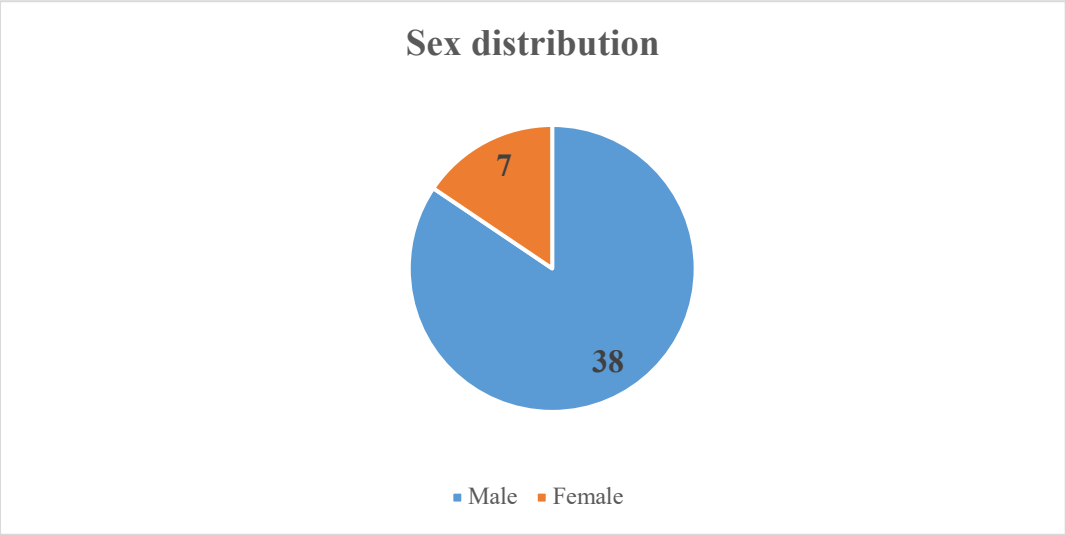

Fig. 11: Frequency distribution of sex in the study population

Age distribution

Table 6: Age distribution in the study population		
Age Group	**Frequency**	**Percent**
<60 years	10	22.22
≥ 60 years	35	77.78
Total	45	100

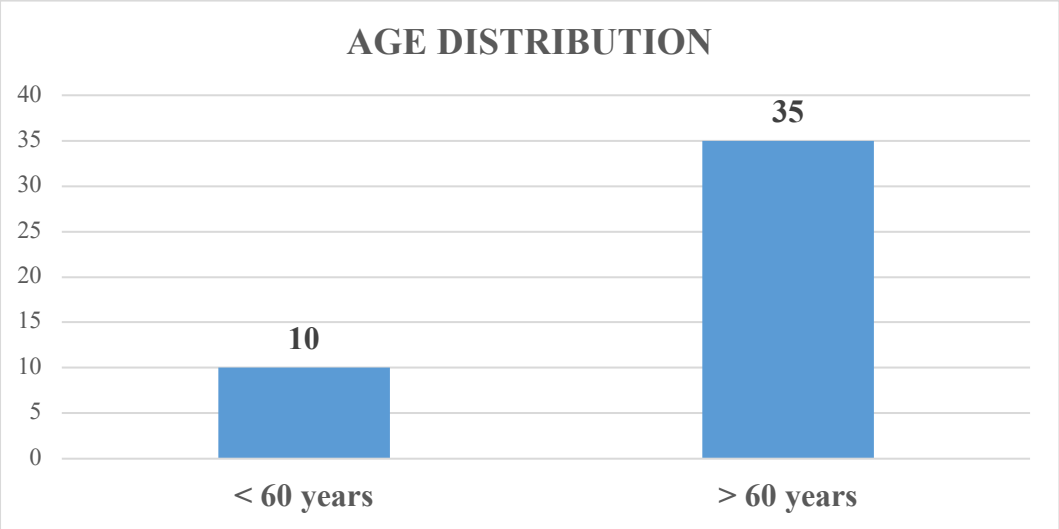

Fig. 12: Age distribution in the study population

RISK FACTORS IN STUDY POPULATION

Table 7: Risk factors in the study population		
Risk Factor	**Present**	**Percentage**
Diabetes mellitus	31	68.89
Hypertension	32	71.11
Smoking	11	24.44
Alcoholism	8	17.78
Coronary heart disease	10	22.22
Dyslipidaemia	20	44.44
Past History of Stroke	19	42.22
Prior TIA	27	60

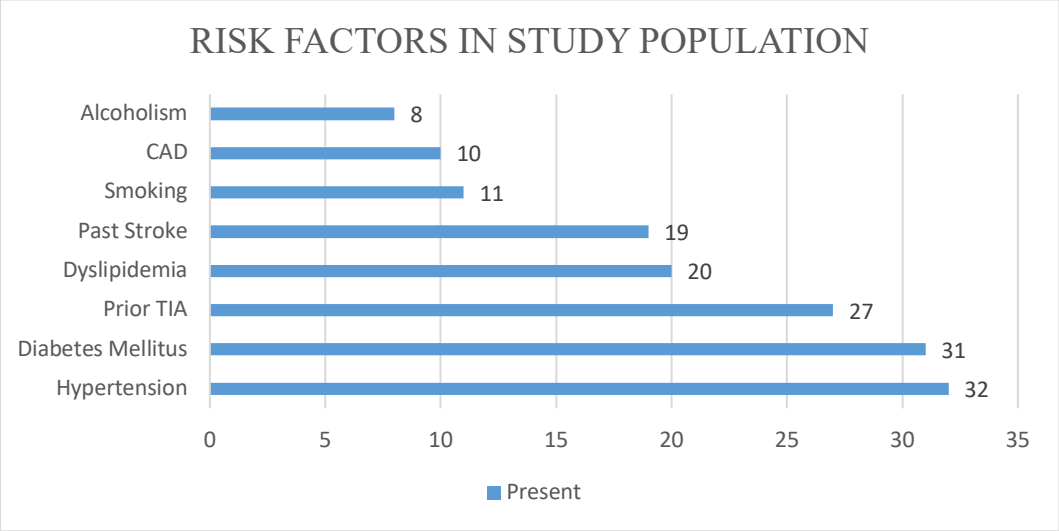

Fig. 13: Risk factors in the study population

Alcohol and tobacco use, diabetes mellitus, hypertension, prior coronary heart disease, dyslipidaemia, renal disease, and past peripheral vascular disease were among the risk factors evaluated in the study population. The most common risk factor in the study population was hypertension (71.1%), followed by diabetes (68.89%) and prior cerebrovascular events (60%).

SIDE OF CEA SURGERY

This study included a good number of subjects with both right (46.67%) and left (53.33%) carotid artery disease.

Table 8: Frequency distribution of ICA endarterectomy

Side	Frequency	Percentage
Right	21	46.67
Left	24	53.33
Total	23	100.0

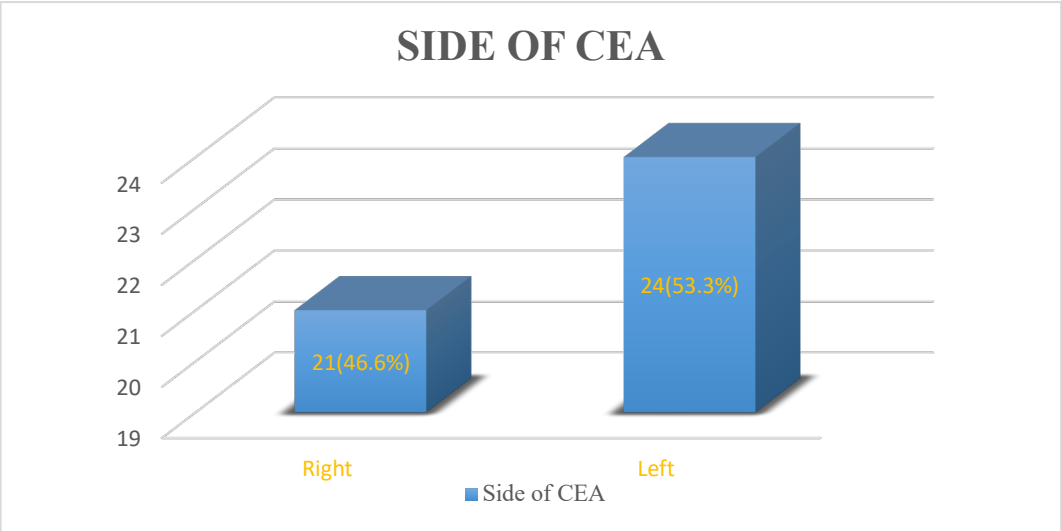

Fig. 14: Frequency distribution of side of carotid endarterectomy

CLINICAL CHARACTERISTICS

The most common presentation was stroke (n=29,64.4%). There were 28.8% previous TIAs among those who developed stroke symptoms. Most common clinical features were facial palsy (86.6%), followed by hemiparesis (31.11%) and dysarthria (20%). Six patients (13.33%) had ipsilateral retinal ischemia at presentation. Hemineglect, aphasia and other cortical symptoms were less encountered in ipsilateral ICA disease.

Table 9: Clinical features in the study population

Clinical features	Frequency	Percent
Amaurosis fugax/ Mono ocular blindness	6	13.33
Facial palsy	39	86.67
Hemiparesis	14	31.11
Hemisensory disturbance	3	6.67
Ataxia	2	4.44
Aphasia	5	11.11
Dysarthria	9	20
Hemianopia	1	2.22

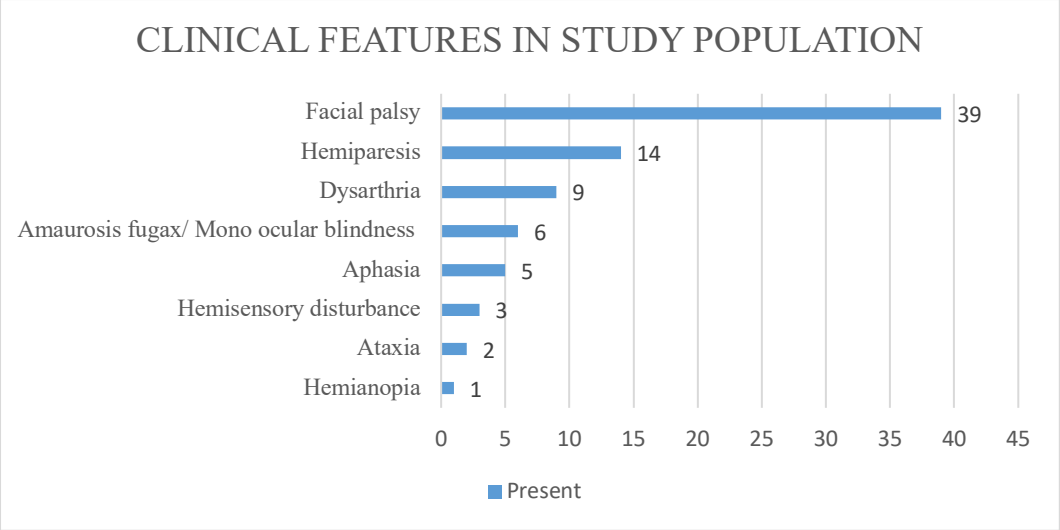

Fig. 15: Frequency distribution of clinical features

Table 10: Clinical presentation in the study population		
Initial event	Frequency	Percent
1. Retinal TIA	3	6.6
2. Hemispheric TIA	10	22.2
3. Stroke	32	71.11
Presenting event	Frequency	Percent
1. Retinal TIA	3	6.6
2. Hemispheric TIA	13	28.8
3. Stroke	29	64.4

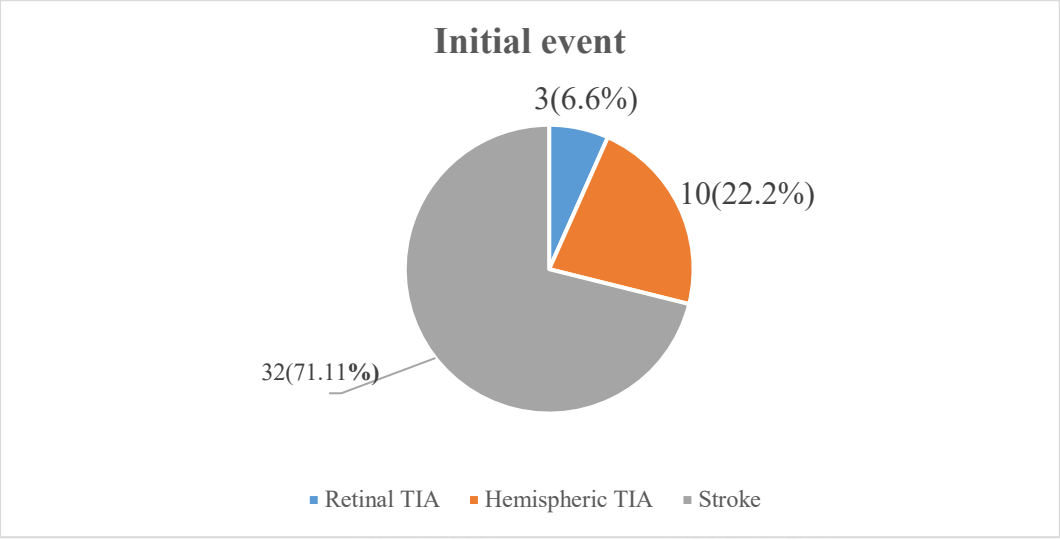

Fig. 16: Frequency distribution of initial clinical event

28.8% of the subjects had prior cerebrovascular events prior to presentation among which 6.6% had retinal TIA and 22.2 % had hemispheric TIA. Majority of the patient had stroke (64.4%) before undergoing surgery.

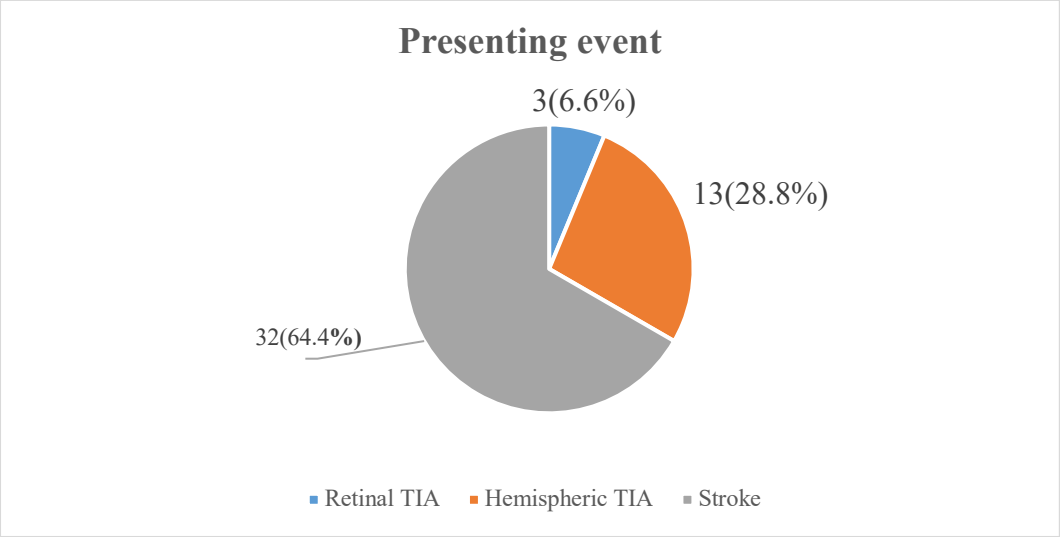

Fig. 17: Frequency distribution presenting clinical event

PRIOR CEREBROVASCULAR EVENTS

The study population's median TIA lasted 5 minutes, and the majority (46.67%) had less than five TIAs before undergoing surgery.

Table 11: Number of TIA in the study population		
Number of TIA	Freq.	Percent
0	18	40.00
1-4	21	46.67
>=5	6	13.33
Duration of TIA in the study population		
TIA (minutes)	Freq.	Percent
1-4	2	4.44
>=5	25	55.56

NIHSS AT PRESENTATION

The median NIHSS score before surgery was 1 (Interquartile range 0-3). Majority (84.44%) of the study population had minor stroke at presentation.

Table 12: NIHSS score before surgery in the study population		
NIHSS score	**Frequency**	**Percent**
0-5	38	84.44
≥ 5	7	15.56

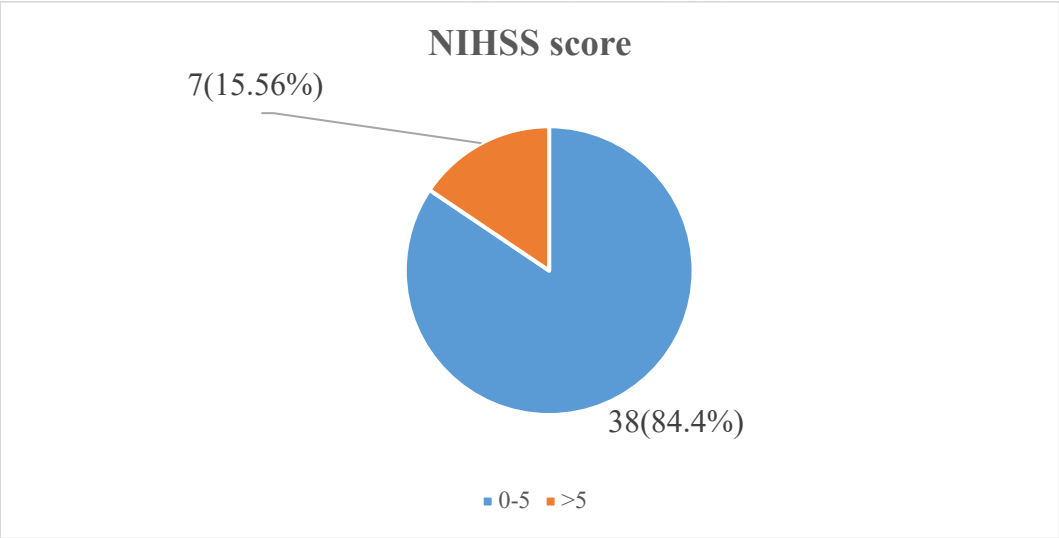

Fig. 18: Frequency distribution of ICA endarterectomy

mRS SCORE BEFORE CEA

Median disability score before undergoing surgery was mRS 1 and only three patients (6.67%) with moderately severe disability (mRS of 4) underwent endarterectomy.

Table 13: mRS score before surgery in the study population		
mRS	Freq.	Percent
0	4	8.89
1	23	51.11
2	10	22.22
3	5	11.11
4	3	6.67

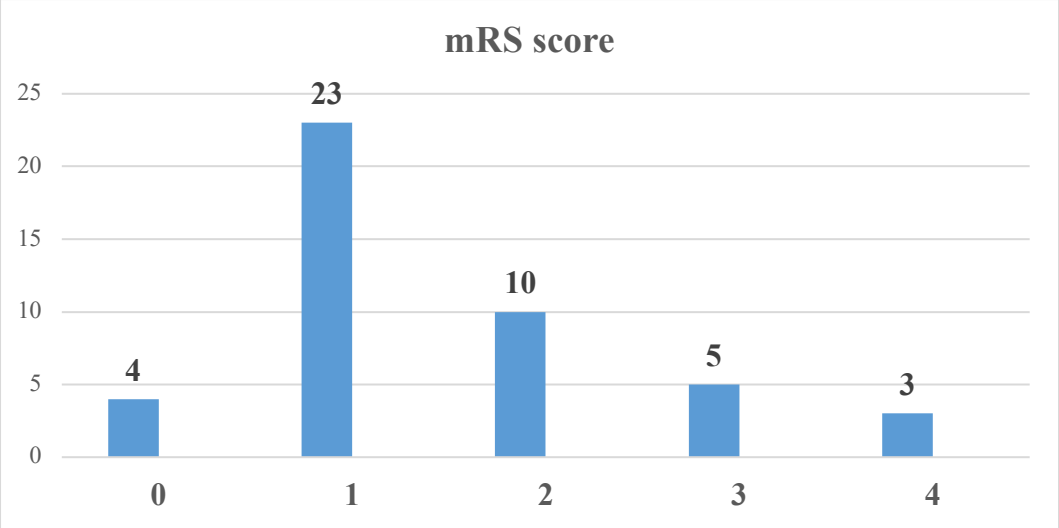

Fig. 19: Frequency distributions of mRS score before surgery

NIHSS AT 3MONTHS

The median NIHSS score before surgery was 1 (Interquartile range 0-3).

Table 14: NIHSS score before surgery in the study population

NIHSS score	Frequency	Percent
0-5	41	93.18
≥ 5	3	6.82

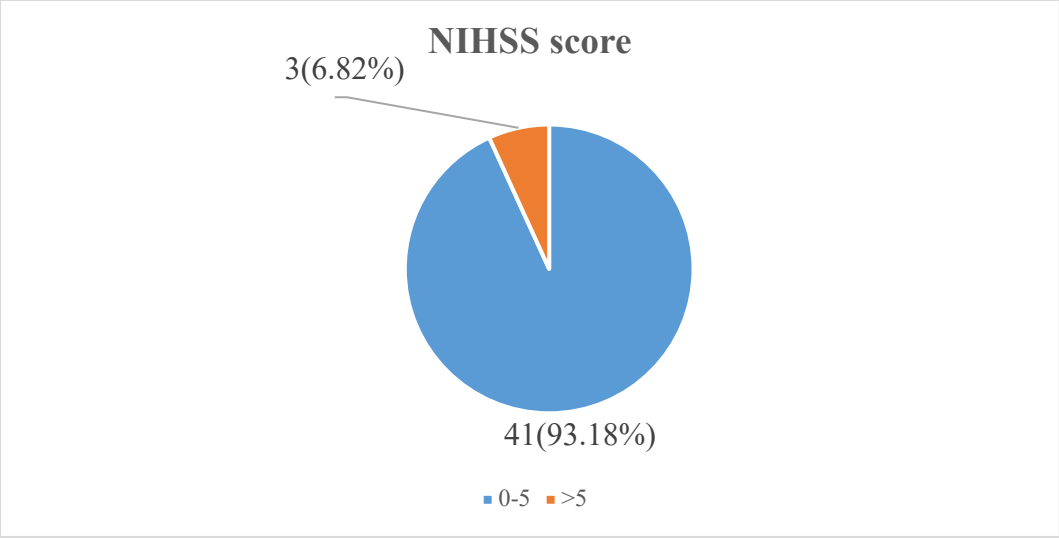

Fig. 20: Frequency distribution of NIHSS at presentation

mRS SCORE AT 3MONTHS

Good functional outcome (mRS 0-2) at three months was seen in 88.89% subjects. Only five (11.11%) had moderate disability at 3 months after the procedure.

Table 15: mRS score at 3 months of follow-up		
mRS	Freq.	Percent
0	31	68.89
1	6	13.33
2	3	6.67
3	5	11.11

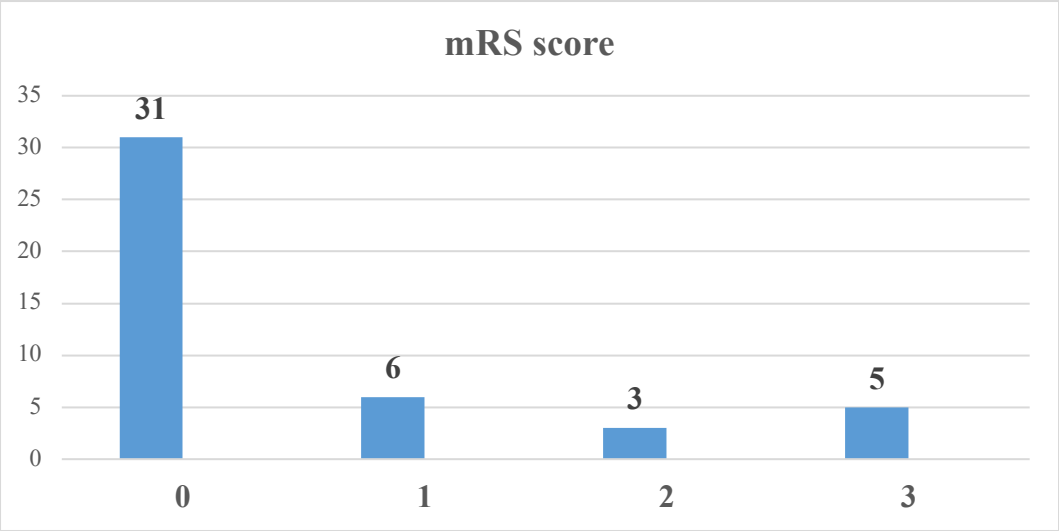

Fig. 21: Frequency distribution of mRS score at 3 months

IMAGING ANALYSIS

The average number of days between having a cerebral ischemic event and having carotid plaque MRI was 57. The average time between MR evaluation and carotid endarterectomy was three days.

CAROTID STENOSIS

In the study population, the majority (90.7%) of the cases had severe (>70%) carotid stenosis. Only 4 individuals had stenosis between 50 and 70 percent. The lowest stenosis was 57%, while the highest was 90%. Contralateral carotid artery occlusion (CCO) were seen in 4 patients (8.8%).

Table 16: Frequency distribution of the degree of carotid stenosis in the study population		
Degree of Carotid Stenosis	**Frequency**	**Percent**
50-70 % stenosis	4	8.88
More than 70% stenosis	41	91.11
Total	45	100.0

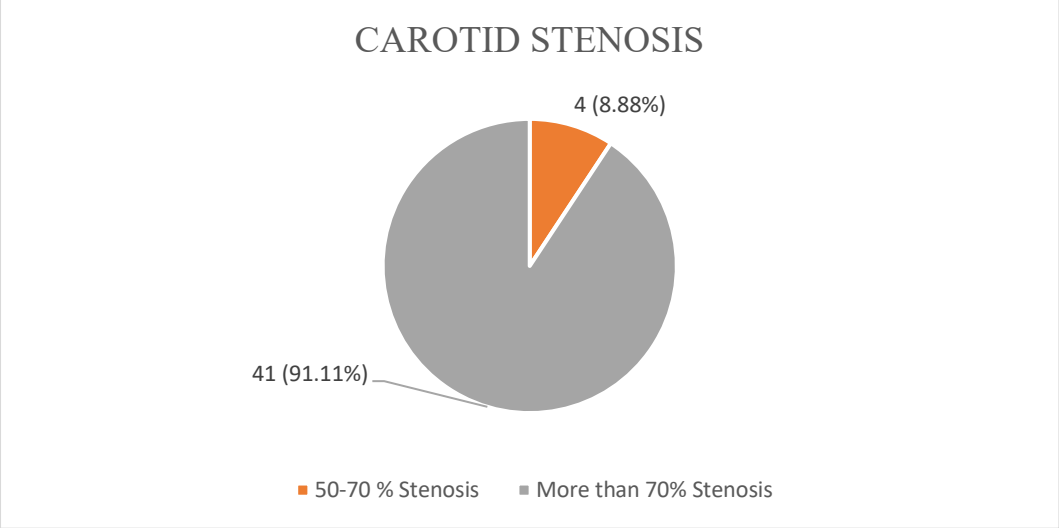

Fig. 22: Frequency distribution of degree of carotid stenosis in the study population

Tandem intracranial (≥ 50%) stenosis of symptomatic side was noted in 10 (24%) subjects.

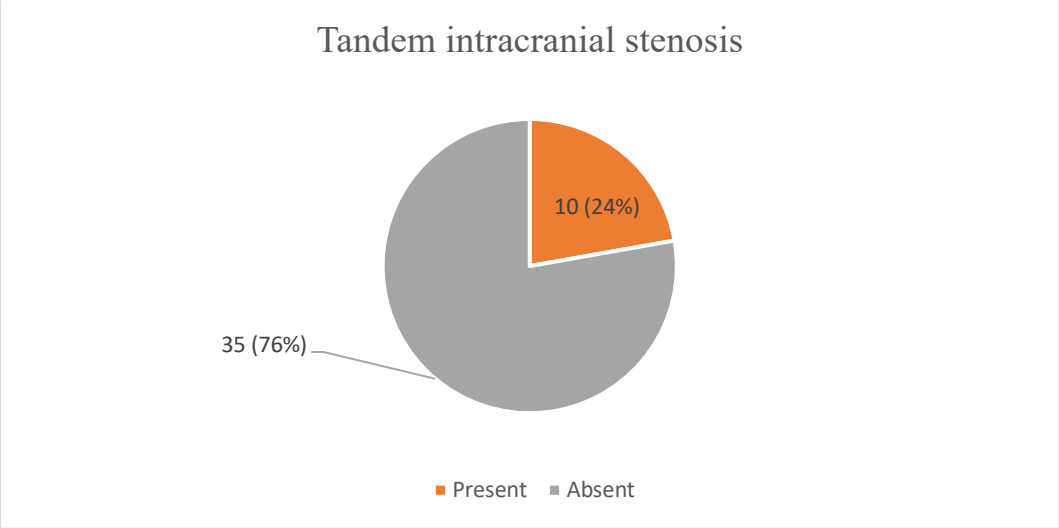

Fig. 23: Frequency distribution of tandem intracranial stenosis (>50%)

CORRELATION OF STENOSIS QUANTIFICATION IN CT AND MRI

A Pearson correlation coefficient of 0.748 (p-value 0.000) was found between the MR and CT assessment of stenosis.

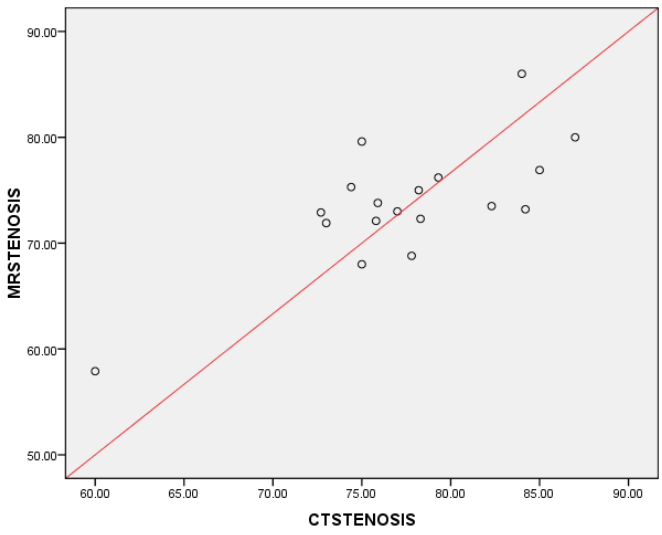

Fig.24: Scatter plot depicting the CT and MR measurements of carotid stenosis in the study population.

INFARCTS PATTERN

Table 17: Infarcts pattern in the study population		
Infarcts	**Frequency**	**Percent**
Single	6	13
Multiple infarcts	32	71
Infarcts Pattern	**Frequency**	**Percent**
Embolic infarcts	29	64%
Hemodynamic infarcts	27	60%
Combination of embolic and hemodynamic infarcts	18	40%
Contralateral infarcts	6	14%

71% of the study population had multiple infarcts and most common pattern of infarcts were embolic (60%) followed by hemodynamic infarcts (60%). Contralateral infarcts were noted in 14% of the patients.

MRI PLAQUE CHARACTERISTICS

Table 18: Frequency distribution of MR plaque characteristics		
MR Plaque Characteristics	**Present**	**Percent**
Calcification	22	48.89
Fibrous plaque	18	40
Lipid rich necrotic core	41	91.11
Intraplaque haemorrhage	24	53.33
Plaque ulceration	18	40
Plaque inflammation	21	46.67

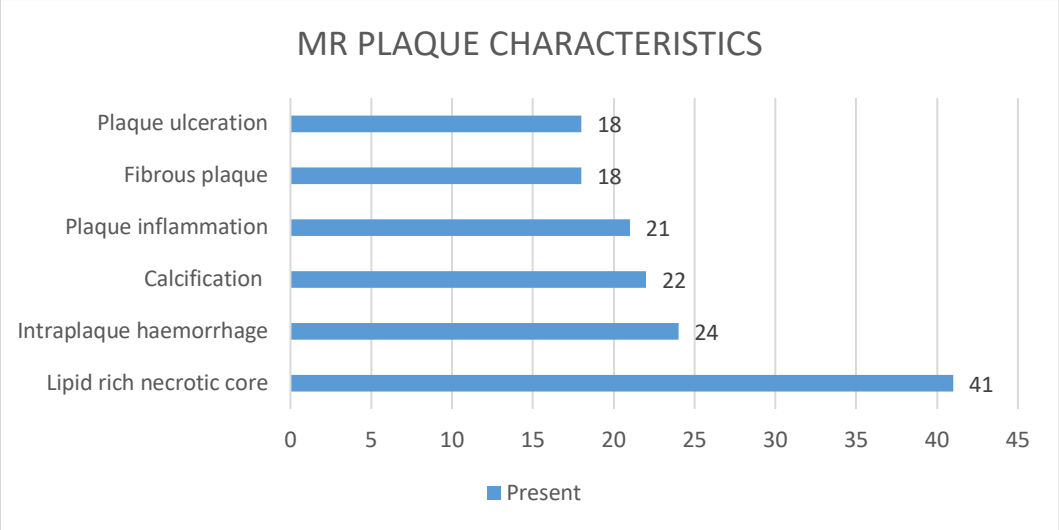

Fig. 25: Frequency distribution of MR Plaque characteristics

The majority of the study group had lipid-rich necrotic core (91.11%) and intraplaque haemorrhage (53.33%), as seen by MR plaque imaging. Intraplaque calcification was seen in 48.89% and there was a good correlation between the calcification assessment made using CT angiography and MR Plaque imaging with a Pearson correlation coefficient of 0.782 (*p-value 0.000*).

Table 19: Frequency distribution of MR plaque characteristics based on Modified AHA classification

Modified AHA classification	Present	Percent
Class V	7	15.56
Class VI	27	60
Class VII	11	24.44

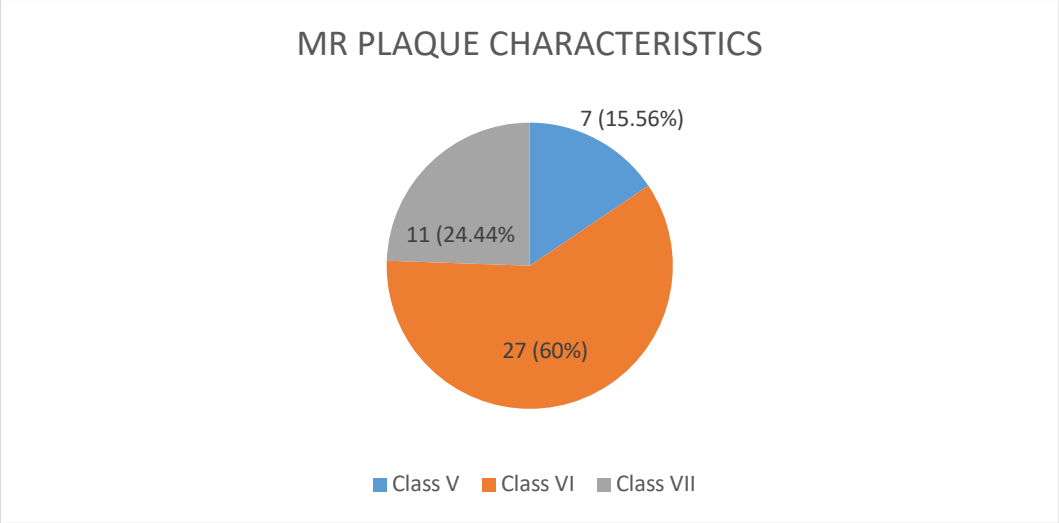

Fig. 26: Frequency distribution of MR plaque characteristics as per Modified AHA classification

60 % of the study population were noted to have complex plaque with possible surface defect, thrombus or haemorrhage (Class VI) and 15.56% with fibrotic plaque (Class VII).

PLAQUE VULNERABILITY BASED ON MR PLAQUE IMAGING

Approximately 2/3rd of the MR data revealed unstable plaque with majority includes lipid rich necrotic core and intraplaque haemorrhage. Few cases had both LRNC and IPH.

Table 20: Frequency distribution of plaque vulnerability based on MR plaque imaging

Plaque vulnerability	Present	Percent
Stable	18	40
Unstable	27	60

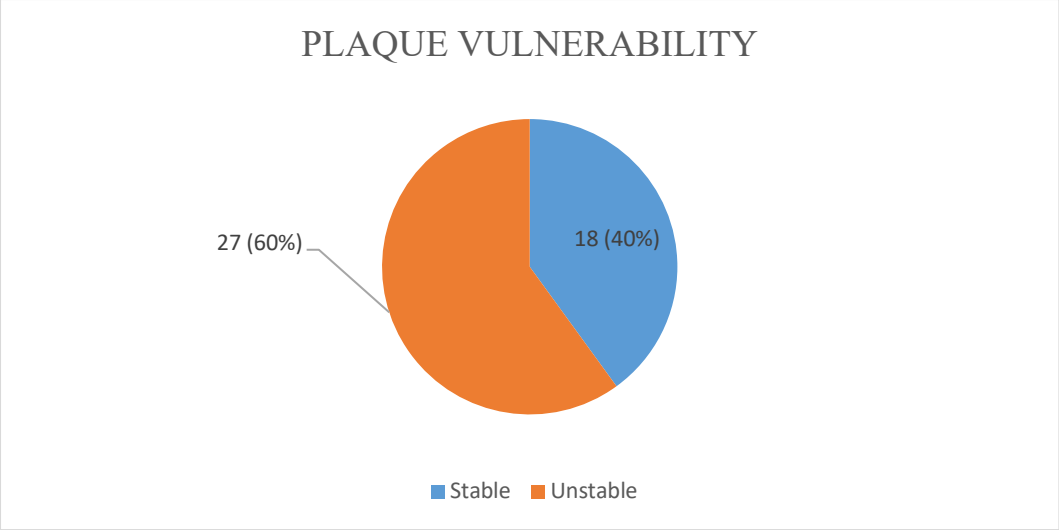

Fig. 27: Frequency distribution of plaque vulnerability based on MR plaque imaging

HISTOPATHOLOGICAL PLAQUE CHARACTERISTICS

A histological examination revealed that 58% of the specimens had features of plaque vulnerability. In descending order, high risk characteristics included a lipid-rich necrotic core (80%), intraplaque haemorrhage (53.33%), and ulceration (46.67%). 31% of the samples had significant plaque inflammation, according to the analysis.

Table 21: Frequency distribution of histological plaque characteristics

Histopathological Plaque Characteristics	Present	Percent
Lipid rich necrotic core	36	80
Intraplaque haemorrhage	24	53.33
Surface thrombosis	5	11.11
Fibrous plaque	5	11.11
Calcification	27	60
Plaque neovascularisation	14	31.11
Cap inflammation	14	31.11
Thin cap (<200 microm)	23	51.11
Ulcerated plaque	21	46.67

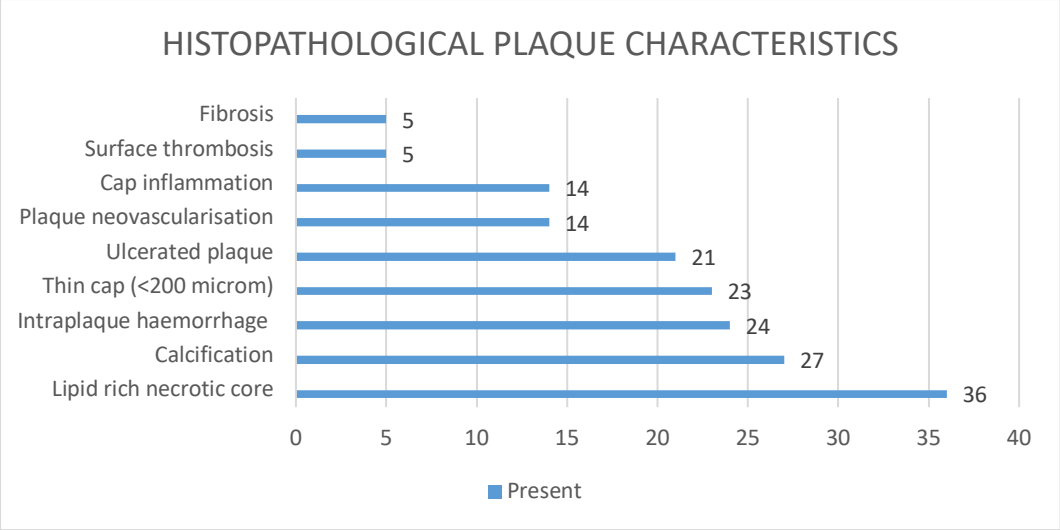

Fig.28: Frequency distribution of histological plaque characteristics

Table 22: Frequency distribution of histopathology plaque characteristics based on AHA classification		
Modified AHA classification	**Present**	**Percent**
Class V	8	17.78
Class VI	26	57.78
Class VII	11	24.44

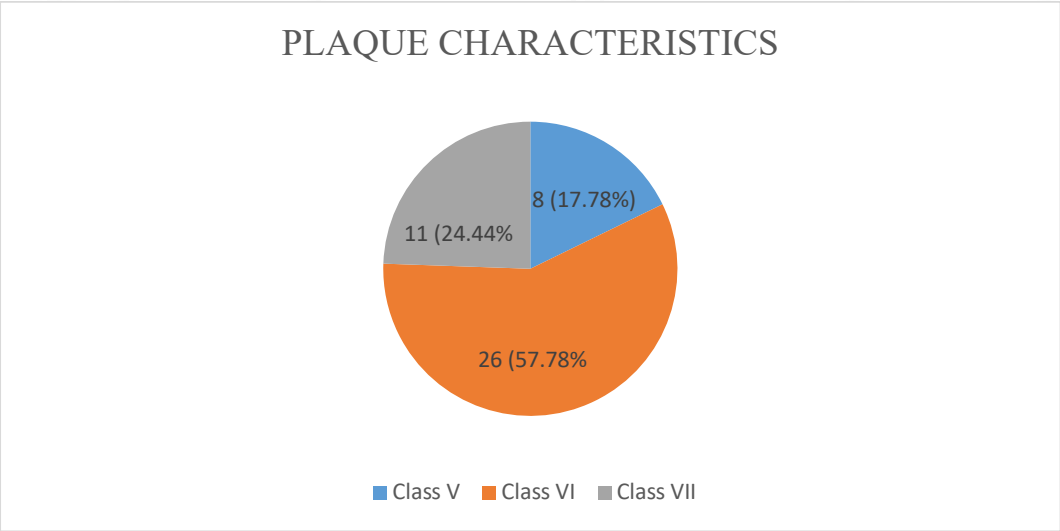

Fig. 29: Frequency distribution of plaque characteristics based of AHA classification

PLAQUE VULNERABILITY BASED ON HISTOPATHOLOGY

Table 23: Frequency distribution of plaque vulnerability based on histopathology		
Plaque vulnerability	**Present**	**Percent**
Stable	19	42.22
Unstable	26	57.77

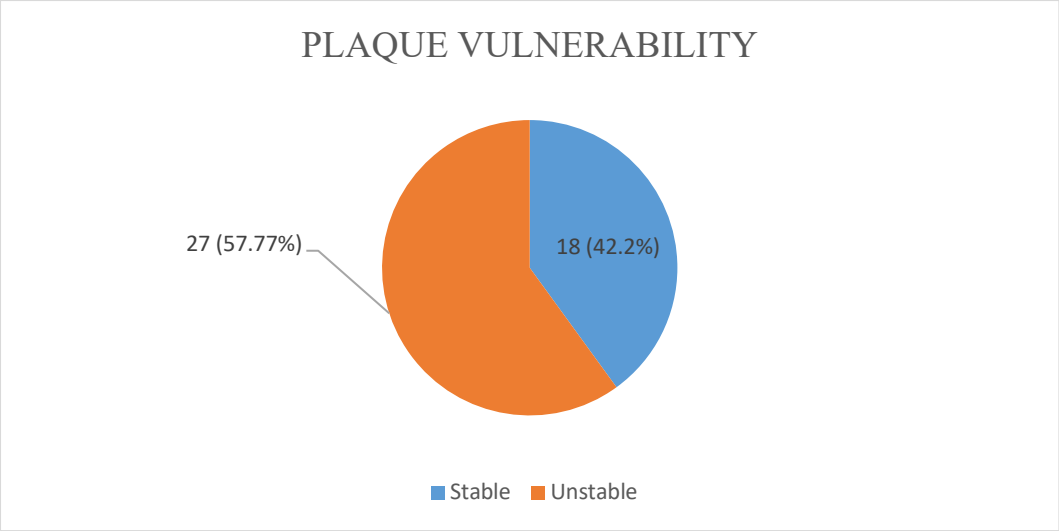

Fig. 30: Frequency distribution of plaque vulnerability

FACTORS ASSOCIATED WITH PLAQUE VULNERABILITY

Table 24: Analysis of risk factor associated with plaque vulnerability			
VARIABLE	**TOTAL (N=45)**	**UNSTABLE PLAQUE**	***p*-value**
Study population	45	26 (57.7%)	
Age			
< 60 years	10	6 (23.07%)	0.278
≥ 60 years	35	20 (76.9%)	
Sex			
Male	38	23 (57.89%)	**0.001**
Female	7	3 (42.86%)	
Hypertension			
Yes	32	17 (53.13%)	0.983
No	13	9 (69.23%)	
Diabetes mellitus			
Yes	31	19 (61.29%)	0.504
No	14	7 (50%)	
Smoking			
Yes	7	6 (85.71%)	**0.001**
No	38	20 (52.63%)	
Coronary heart disease			
Yes	10	6 (60%)	0.026
No	35	20 (57.14%)	
Dyslipidaemia			
Yes	20	11 (55%)	0.113
No	25	15 (60%)	
Alcoholism			
Yes	8	2(25%)	0.285
No	37	24 (64.86%)	
Number of prior TIAs			
< 5	39	21(53.84%)	**0.001**
≥ 5	6	5 (83.33%)	
Duration of TIA			
1-4 minutes	20	11(55%)	0.136
≥ 5minutes	25	15 (60%)	
Severity of stroke (NIHSS)			
0-4	38	22 (57.89%)	**0.001**
≥ 5	7	4 (57.14%)	
Prior cerebrovascular events			
Absent	9	5 (55.56%)	**0.001**
Either TIA/Stroke	36	21 (58.33%)	
Type of presenting event			
Retinal TIA	3	2 (66.66%)	0.023
Hemispheric TIA	10	6 (60%)	
Stroke	32	18 (56.25%)	
Degree of stenosis			
< 70%	4	2 (50%)	**0.001**
≥ 70%	41	24 (58.5%)	
Ipsilateral intracranial stenosis (≥ 50%)			
Yes	10	6 (60%)	0.023
No	35	20 (57.14%)	

GLYCAEMIC CONTROL WITH PLAQUE VULNERABILITY

Table 25: Analysis of glycaemic control with plaque vulnerability					
	Plaque Status	**N**	**Mean**	**Std. Error Mean**	**p-value**
Serum RBS	Vulnerable	26	171.96	11.88	0.241
	Non vulnerable	19	159.21	13.33	
HbA1c	Vulnerable	26	7.57	0.28	0.207
	Non-vulnerable	19	7.23	0.29	

LIPID PROFILE WITH PLAQUE VULNERABILITY

Table 26: Analysis of lipid profile parameters with plaque vulnerability					
	Plaque Status	**N**	**Mean**	**Std. Error Mean**	**p-value**
TOTAL CHOLESTEROL	Vulnerable	26	138.8	6.12	0.496
	Non vulnerable	19	128.7	7.12	
LDL	Vulnerable	26	79.96	5.87	0.497
	Non-vulnerable	19	65.89	6.21	
TG	Vulnerable	26	100.03	7.26	0.211
	Non-vulnerable	19	90.47	9.55	
HDL	Vulnerable	26	41.42	2.84	0.138
	Non-vulnerable	19	45.21	2.22	

Total cholesterol, LDL, and triglyceride levels were high in patients with pathologically vulnerable plaques, although HDL levels were greater in the non-vulnerable group. The difference in mean values, however, was not statistically significant ($p > 0.01$).

ASSOCIATION OF NUMBER OF THROMBOEMBOLIC EVENTS AND PLAQUE VULNERABILITY

Table 27: Analysis of prior cerebrovascular events with plaque vulnerability			
NO OF PRIOR CEREBROVASCULAR EVENTS			
	Study Subjects	Mean	Std. Error Mean
Vulnerable	36	5.6875	0.48921
Non vulnerable	9	2.0000	0.75593

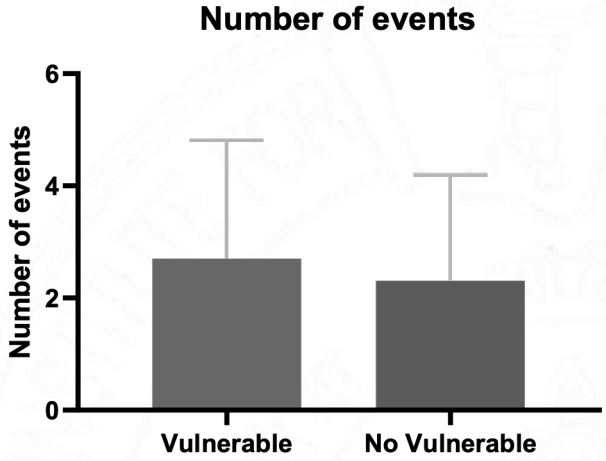

Fig.31: Analysis of prior cerebrovascular events with plaque vulnerability

Though the mean number of events was found to be higher for the subjects who had vulnerable plaque compared to the non-vulnerable plaque group, this was not statistically significant.

CORRELATION OF MRI WITH HISTOLOGY

Lipid Rich Necrotic Core

The detection of lipid necrotic core with MR plaque imaging compared to histopathology showed moderate agreement (kappa 0.697), with 92.11% sensitivity and 85.71% specificity.

Table 28: Comparison of MR and histological detection of lipid rich necrotic core in carotid plaque

MR – Lipid Necrotic Core		Histology - Lipid rich necrotic core		Total
		Absent	**Present**	
	Absent	6	3	9
	Present	1	35	36
	Total	7	38	45
Kappa value : 0.697(Moderate agreement); p Value 0.000				

Sensitivity	92.11
Specificity	85.71
Positive Predictive Value	97.22
NPV	52.89
Accuracy	84.44

Intra-plaque Haemorrhage

The detection of intraplaque haemorrhage with MR plaque imaging compared to histopathology showed moderate agreement (kappa 0.774), with 91.3 % sensitivity and 86.36 % specificity. Among all the unstable plaque characteristics, the diagnostic accuracy for intraplaque haemorrhage identification utilising MR plaque imaging was the highest.

Table 29: Comparison of MR and histological detection of intraplaque haemorrhage in carotid plaque				
MR Intraplaque haemorrhage		**Histology – Intraplaque haemorrhage**		Total
		Present	**Absent**	
	Present	21	3	24
	Absent	2	19	21
	Total	23	22	45
Kappa value : 0.774 (Strong agreement); p Value 0.000				

Sensitivity	91.3
Specificity	86.36
PPV	87.5
NPV	90.48
Accuracy	91.3

Ulcerated plaque

Ulcerated plaque was found in 46.67% in the histological analysis and 40% on MRI. MRI showed moderate to high sensitivity (84.62%) and specificity (78.12%) in predicting plaque ulceration. Congruence was moderate and statistically significant ($\kappa = 0.563$, $p < 0.001$).

Table 30: Comparison of MR and histological detection of ulceration in carotid plaque				
MR – Ulcerated plaque		**Histology – Ulcerated plaque**		Total
		Present	**Absent**	
	Present	11	7	18
	Absent	2	25	27
	Total	13	32	45
Kappa value : 0.563 (moderate agreement); p Value 0.000				

Sensitivity	84.62
Specificity	78.12
PPV	61.11
NPV	92.59
Accuracy	91.3

Fibrous plaque

Table 31: Comparison of MR and histological detection of fibrosis in carotid plaque				
MR – Fibrous Cap		Histology – Fibrous Cap		Total
		Present	Absent	
	Present	4	1	5
	Absent	23	17	40
	Total	27	18	45
Kappa value : 0.258 (Fair agreement); Approx Sig 0.1665				

Sensitivity	80
Specificity	42.5
PPV	14.81
NPV	87.75
Accuracy	56.5

There was a relatively low prevalence of fibrous cap in histological analysis (11.11%), whereas MRI showed fibrous plaque in 40 %. Sensitivity (80%) and specificity (42.5%) were poor and there was no significant congruence between MRI and histology ($\kappa = 0.258$, $p = 0.1665$).

Overall plaque vulnerability

Table 32: Comparison of MR and histological detection of overall plaque vulnerability in carotid plaque				
MR – Plaque Vulnerability		Histology – Plaque Vulnerability		Total
		Vulnerable	Non-vulnerable	
	Vulnerable	24	3	27
	Non vulnerable	2	16	18
	Total	26	19	45
Kappa value : 0.7706 (Moderate agreement); p : 0.000				

Fig.22: Comparison of MR and histological detection of overall plaque vulnerability in carotid plaque

Sensitivity	92.31%
Specificity	84.21%
PPV	88.89%
NPV	88.89%
Accuracy	86.96%

The study demonstrated a high level of agreement in detecting intraplaque haemorrhage, but only a moderate level of agreement in detecting the lipid-rich necrotic core and overall plaque vulnerability (kappa 0.7706). There only appeared to be a slight concordance between MR and histology in detecting fibrous cap integrity.

PERIPROCEDURAL ISCHEMIC EVENTS

Only two patient had periprocedural cerebral ischemic events (4.44%) and both patient had hemispheric TIA. There was no periprocedural cardiac event or mortality.

In view of the small number of events, its correlation to plaque vulnerability couldn't be analysed.

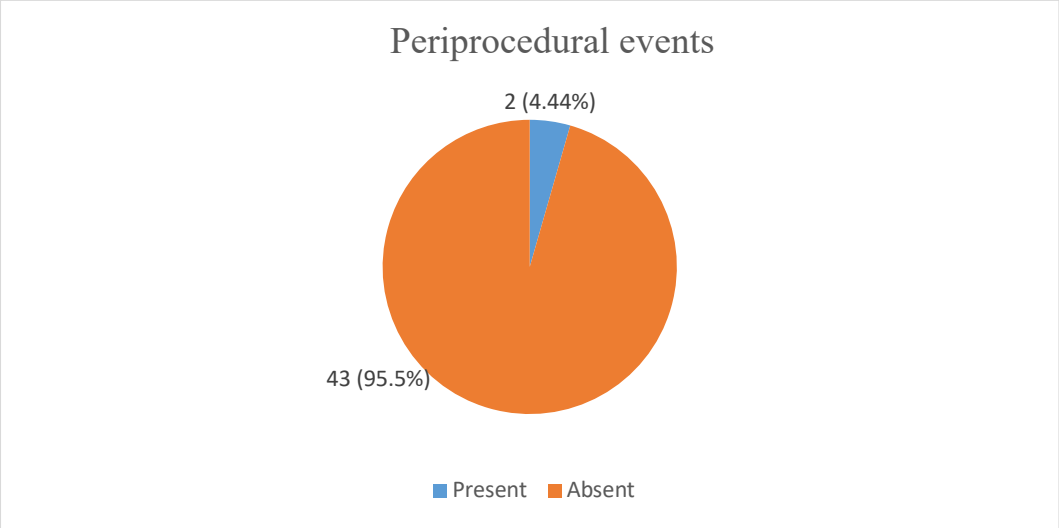

Fig. 32- Frequency distribution of periprocedural events

DISCUSSION

DISCUSSION

In the past two decades, there has been a paradigm shift in how carotid atherosclerotic disease is understood, with the emphasis shifting from the severity of luminal narrowing to the inherent characteristics of plaque morphology. Other than the existence of ulcerations, conventional angiography, such as CT and MR angiography, is unable to evaluate the morphological characteristics of plaque. As a consequence, an imaging method is needed that is able to provide plaque composition in addition to degree of stenosis. Magnetic resonance imaging (MRI) is the standard imaging technique for assessing such plaques in vivo which is currently the most accurate and versatile method. MRI enables radiologists to assess for several vulnerable characteristics of plaques, such as intraplaque haemorrhage, lipid-rich necrotic core, and ulceration. Nevertheless, MR carotid plaque imaging is a dynamic and complex that demands in-depth understanding of the histopathological basis of various imaging results as well as the immediate and prognostic implications of vulnerable plaque characteristics. Initial study by Watanabe et al which compared 1.5T MR imaging with histology showed the sensitivity, specificity and accuracy of 96%, 93% and 94% respectively, for diagnosing vulnerable plaque features. The detailed information of plaque segments revealed by slice-by-slice MR examination of the carotid wall correlated well with the features of corresponding histologic sections (80). Another study by Moody, Alan R et al showed sensitivity and specificity of 84%, negative predictive value of 70%, and positive predictive value of 93% wherein they used 1.5 Tesla 3D T_1-weighted imaging of the carotid vessels in patients with symptomatic ICA disease and histologically confirmed unstable plaque. The high contrast generated by short-T_1 signals within the plaque allows for ease of interpretation, making this technique highly applicable in the research and clinical setting for the investigation of carotid atherosclerotic disease (81). In clinical radiology, a new generation of 3T MR imaging is currently in use. When compared to 1.5-T carotid plaque imaging, high-spatial-resolution carotid plaque

imaging at 3.0 T shows significant improvements in signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and image quality. Ota, Hideki et al. found sensitivity, specificity of 80% and 97% respectively with k values 0.80 for 3T magnetization prepared RAGE imaging compared with histopathology for vulnerable plaque features. Compared with the results of previous studies of 1.5-T MR imaging , there is consistently higher specificity and similar or better overall agreement in the detection of unstable plaque features with 3T imaging. The improved specificity at 3T can be attributed to the lower false positive result rate, which was caused by areas of high signal intensity of fibrous tissue and also to better signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and image quality.

This study aimed to determine the diagnostic accuracy of 3T MR plaque imagine as compared to histopathology and clinical relevance of the high risk plaque characteristics. To the best of my knowledge, our study is the only one that compared histology and 3T MR plaque imaging with post contrast images. In total, 47 subjects had undergone endarterectomy after carotid plaque MRI as part of the study. 2 patients were ultimately eliminated from the analysis due to poor quality of images due to motion artefacts leaving 45 subjects available for final analyses.

DEMOGRAPHICS AND TIMING OF CEA

The mean age was 65.06 $\pm$ 7.7 years, with 77.8% of the subjects being over the age of 60 which is comparable to the Indo- US Collaborative Stroke Project registry (58.3±14.7 years) (1). The percentage of women (15.56%) was significantly lower than that of Western and Chinese populations. The fact that fewer women seek medical care may also be due to cultural bias, as men are more likely to do so. The median age of our study population was 66 years. The youngest patient was 45 years, with him being the only young stroke patient in the study. This was also the case with most registry data on stroke (73). The average time to CEA was 57 days (SD $\pm$ 46). Our study provides evidence from the real world on the timing of CEA, data that emphasises the delay rather than the guideline-recommended timing of less than two weeks.

Only 17.7% of patients in our group underwent CEA within two weeks, compared to the western data, which showed that 39–72% of patients underwent early CEA (74-77).

RISK FACTORS

The most common risk factor in the study population was hypertension (71.1%), followed by diabetes (68.89%) and prior cerebrovascular events (60%). In comparison to Western populations, we observed that hypertension and diabetes was higher in our study population.

PLAQUE CHARACTERISTICS IN 3T MR IMAGING

LIPID NECROTIC CORE

MRI showed excellent sensitivity (92.11%) and specificity (85.71%) for lipid rich necrotic core with moderate agreement (k 0.697). Previous studies mostly used T1W sequences to recognise LRNC. When considering LRNC areas, Saam et al. utilised comparable sequences, and the sensitivity and specificity were 92% and 65%, respectively, with k 0.73 and there was a strong correlation between the histology and MRI (P 0.001)(34). However, Touze et al.'s study(86) described significant inter-observer variability in the detection of the lipid component, which would account for the study's modest agreement as opposed to the stronger relationship with haemorrhage detection. Additionally, in the studies mentioned above, administering contrast improved the ability to detect the necrotic core. In-addition, diffusion-weighted imaging with ADC value assessment, which showed a substantial difference in the identification of the lipid necrotic plaque, may help to resolve this problem, though.

INTRAPLAQUE HEMORRHAGE

Neoangiogenesis with leaky arteries within the plaque is thought to contribute to intraplaque haemorrhage(80). Our findings suggest a moderate agreement (kappa 0.774) between the detection of intraplaque bleeding by MR plaque imaging and histopathology, with 91.3% sensitivity and 86.36% specificity. The spoiled gradient 3D sequence in CUBE T1 that we used

for evaluation has the benefit of haemorrhage detection as well. This was in line with a previous meta-analysis by Zhou et al., which found that MR had an overall sensitivity and specificity of 87% and 92% for haemorrhage detection(81). Cerebrovascular events had a hazard ratio of 5.69 in the presence of IPH, and the overall annualised event rate was 17.71% (82). As in our investigation, the majority of the studies in the meta-analysis used a 1.5 T MRI and mostly contrast sequences. With encouraging results, MP-RAGE and SNAP, two more recent sequences, have been tested for the identification of haemorrhage, particularly in the carotids(51,84). Even in symptomatic patients with >50% stenosis, finding the absence of haemorrhage in a carotid plaque is clinically significant because it suggests a benign course of the illness (85). Previous studies have characterised the low ADC values in IPH and made the assumption that they were caused by the inflammatory nature of the plaque and the presence of LRNC(48).

ULCERATION

Ulcerated plaque was found in 46.67% in the histological analysis and 40% on MRI. MRI showed moderate to high sensitivity (84.62%) and specificity (78.12%) in predicting plaque ulceration. Congruence was moderate and statistically significant ($\kappa = 0.563$, $p < 0.001$).

Albuquerque et al. in his study also revealed no significant association when the TOF signal characteristics in the assessment of fibrous cap thickness(p=0.38) (83). Non-contrast assessment of fibrous cap is limited by the spatial resolution of MRI to the actual thickness of the cap. The utility of MR evaluation of carotids may also be done as a marker for risk stratification for cardiovascular events as well.

OVERALL PLAQUE STABILITY

In our study, patients with symptomatic stenosis higher than 50% were assessed with a high possibility of encountering complex plaque. We found evidence of plaque vulnerability (lipid-rich necrotic core, ulceration and haemorrhage) in 57.7%. of histopathological sections. MRI recognised these signals with high levels of sensitivity (92.31%) and specificity (84.21%). MRI proved to have high specificity and sensitivity in the identification high risk plaque characteristics. Our result supports the literature by demonstrating that the combined evaluation of T1 and TOF sequences is crucial to distinguishing between lipid core and intraplaque haemorrhage. Although both the haemorrhage and the lipid core are hyperintense on T1, the haemorrhage can be differentiated due to its hyperintensity in the TOF sequences, which are the best discriminators. On T2 and PD, however, the appearances of the lipid core and haemorrhage varied greatly, primarily manifesting as regions of hypo- or isointensity in comparison to the surrounding muscle. Therefore, while choosing a plan of treatment for these patients, it is important to consider both the type of plaque present and the degree of stenosis present. Vulnerable plaque, even in the absence of significant stenosis, may warrant interventional therapy rather than medical therapy alone. Additionally, based on the risk of embolism, the information on plaque morphology could be utilised to decide between open and endovascular surgery, which can also affect the choice of the cerebral protective device to be used. Instead, MRI might play a key role in tracking the evolution of lesions over time in the setting of medical therapy.

	G. Puppini et al. [78] (n= 15)			Tapis pascal et al. [79] (n=25)			Present study (n=45)		
	Sn	Sp	kappa	Sn	Sp	kappa	Sn	Sp	kappa
Lipid rich necrotic core (LRNC)	91.6%	95%	0.848	72.7%	100%	0.39	92.1%	85.7%	0.697
Intraplaque haemorrhage (IPH)	91.6%	100%	0.945	72.2%	71.4%	0.386	91.3%	86.6%	0.774
Ulceration	NA	NA	NA	57.1%	44.4%	0.012	84.6%	78.1%	0.563
Calcification	80%	93.7%	0.652	81.8%	66.6%	0.339	92.3%	84.2%	0.674

Sn- Sensitivity, Sp- specificity, NA- not available

Table 33. Plaque morphology components and diagnostic accuracy of MR plaque imaging in previous studies

CLINICAL CHARACTERISTICS

The most common presentation was stroke (n=29,64.4%). Of those who had presented with stroke, 28.8 % had prior TIAs including retinal TIAs (6.6%). The median NIHSS score before surgery was 1 (Interquartile range 0-3). Majority (84.44%) of the study population had minor stroke at presentation. The key findings of our study were the high-grade stenosis in the symptomatic carotid of a significant number of our patients for carotid endarterectomy who arrived late after the ischemic event, typically after a stroke rather than TIA. Despite 28.8 % of our patients having prior TIAs, about two-thirds of them presented after a stroke. Patients might overlook the seriousness of the condition and frequently ignore it until they experience a stroke because they fully recover after a TIA. A previous Indian study found that factors influencing endarterectomy delay included patients' failure to recognise stroke symptoms, delays in seeking medical attention and referral to a stroke neurologist or vascular surgeon, delays in making the decision, getting a second opinion from a different specialist, and financial constraints (28). According to a study from Pakistan, 15% of individuals with carotid stenosis were not aware that surgery was an option (29). Another large retrospective study by Naveen Kumar et al. showed that large proportion of our patients for carotid endarterectomy presented late after the ischemic event, mostly after a stroke rather than TIA,

and none of the clinical or imaging features including co-existent tandem significant intracranial atherosclerotic disease, or a contralateral carotid occlusion predicted perioperative cerebral ischemic events (83). Our findings were consistent with a small number of studies conducted in Asian nations, where strokes were the most common form of presentation (30-33). This contrasts with the western world, where after a hemisphere or retinal TIA, more than 50% of patients undergo CEA (34-37).

CAROTID STENOSIS WITH CT AND MRI

Majority (90.7%) of the cases had severe (>70%) carotid stenosis and Tandem intracranial (≥ 50%) stenosis of symptomatic side was noted in 24% subjects. When compared to the Western world, the Asian population have a higher prevalence of intracranial atherosclerosis, with around 18-48% of individuals having co-existing substantial intracranial and extracranial atherosclerotic disease (38,39). Our findings confirmed the previous findings, with approximately one-fourth of our group exhibiting significant co-existing tandem cerebral atherosclerosis. Our findings were consistent with a large single-centre Italian study that found no difference in the frequency of perioperative events between CEA patients with and without co-existing simultaneous cerebral atherosclerosis (41). 8.8% patients had a contralateral carotid artery occlusion in the present study. In dearth of randomised controlled trials, the choice of carotid revascularization in patients with contralateral carotid occlusion remains controversial, with some research supporting CEA (42,43) and others favouring carotid artery stenting (CAS) (44,45). In such patient populations, the Western world favours CAS over CEA; yet none of our patients with a contralateral carotid occlusion developed a periprocedural problem. This finding is reassuring because it suggests that CEA is a safe procedure in these patients.

CTA and MRA stenosis measures demonstrated a good correlation (Pearson correlation coefficient 0.748) in our study, confirming the majority of the studies available in the literature. According to a meta-analysis, the overall sensitivity and specificity of TOF MRA

for diagnosing severe stenosis are 91.2% and 82.3%, respectively(75). In another investigation, Lell et al found a remarkable concordance between CTA and MRA TOF (difference 0.6%; CI: -3,4.3%)(76). CTA and MRA are reported to be equally sensitive but varied in specificity, with CTA always having a higher specificity(77). MRA suffers from flow signal loss, particularly in turbulent and slow flow, resulting in an inaccurate determination of stenosis degree. In this case, contrast-enhanced MRA is superior. Compared to conventional MRA, contrast-enhanced MRA was found to have 7% and 11% higher sensitivity and specificity in diagnosing carotid artery stenosis of 70% or above (78). Compared to Doppler sonography or MRA, CTA exposes patients to more radiation, especially those with mild to moderate stenosis who will need frequent imaging follow-up.

ASSOCIATION OF CLINICAL CHARACTERISTICS WITH PATHOLOGICAL PLAQUE VULNERABILITY

On univariate analysis, elderly age group (>60 years), male sex, smoking and degree of stenosis were the risk factors significantly correlated with the presence of unstable carotid plaques, which are characterised by a high degree of inflammation, thinning, and rupture of the cap associated with an acute thrombosis. In addition a significant correlation was also observed between the number of TIAs and prior cerebrovascular events. Contrary to a study by Rovella et al., which found a correlation between the identification of unstable plaques and hypertension, dyslipidaemia, and male gender (74), none of the conventional risk factors were related with high risk plaque features in the present study. Mean values of total cholesterol, LDL, and triglyceride levels were high in patients who had a pathologically vulnerable plaque, whereas HDL mean was higher in the non – vulnerable group. However, the difference in mean values was not statistically significant ($p > 0.01$).

STRENGTH OF THE STUDY

The study employs a comparative design by comparing the diagnostic accuracy of MR carotid plaque imaging with a well-regarded reference standard – histopathology. The study demonstrates strong diagnostic accuracy of MR carotid plaque imaging compared to histopathology, it could lead to improvements in non-invasive diagnostic techniques for carotid artery stenosis. It provides valuable information for risk stratification , treatment planning and may provide valuable information regarding periprocedural risk.

LIMITATIONS

1. The lack of modern motion correction processes may have also influenced image acquisition.
2. Inter and intraobserver variability was not tested in this study, which would have determined the modality's reliability. Furthermore, the analysis was simply qualitative and quantitative analysis of the size/percentage volume lipid-rich necrotic core/haemorrhage was not assessed.
3. Imaging and histopathology were not performed simultaneously in few patients, leading to discrepancies in the observed findings. Plaque characteristics could change between the imaging and histopathology procedures, affecting the diagnostic accuracy.
4. The absence of standardized imaging and histopathological protocols across different centres can lead to inconsistencies and hinder comparisons between studies.

CONCLUSION

CONCLUSION

MR carotid plaque imaging has shown promising diagnostic accuracy compared with histopathology in assessing plaque morphology and composition in patients with symptomatic carotid artery stenosis. The MR plaque imaging is capable of identifying the unstable plaque characteristics with high sensitivity and specificity.

There is substantial delay noted in patients undergoing CEA with the majority presenting just after a stroke which is the real world scenario.

CEA can be performed safely in individuals with contralateral carotid blockage and tandem intracranial atherosclerotic lesions.

It provides valuable information for risk stratification and treatment planning.

Carotid plaque imaging play crucial role in deciding treatment options for asymptomatic carotid stenosis and in the workup of patients with Embolic stroke of unknown source (ESUS) as well.

A good correlation was noted between CT angiography and 3D TOF MR angiography assessment of carotid stenosis.

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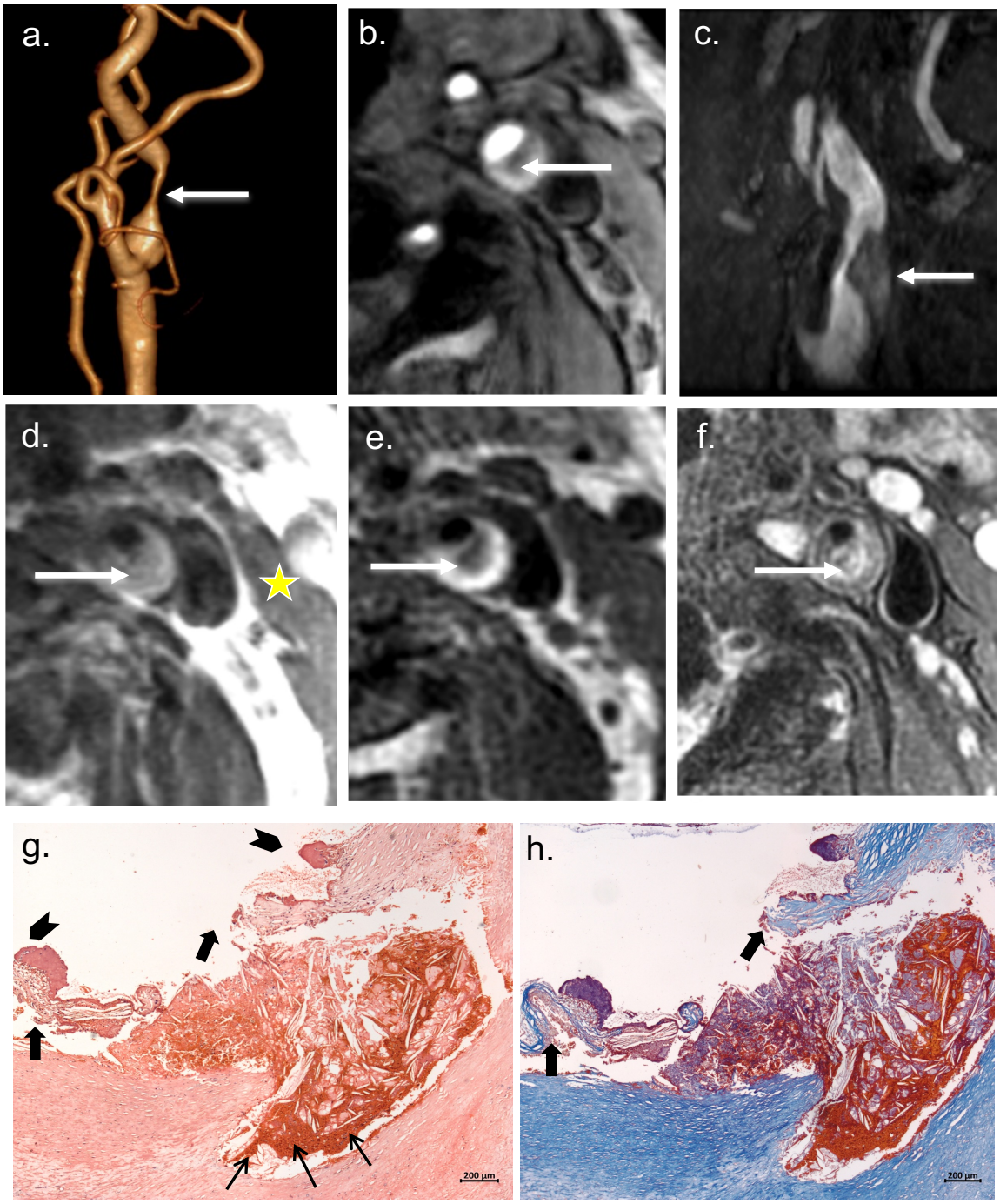
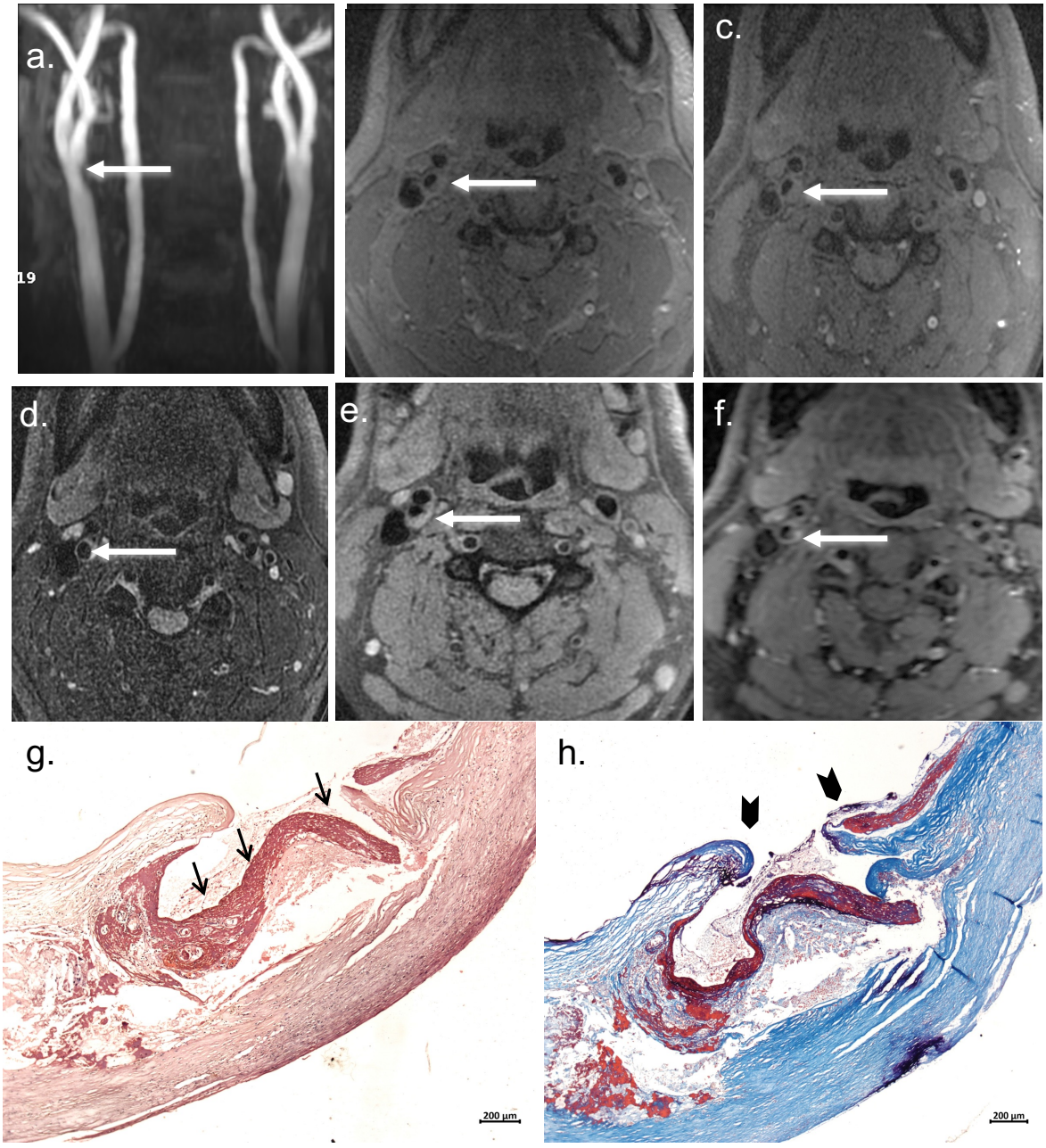
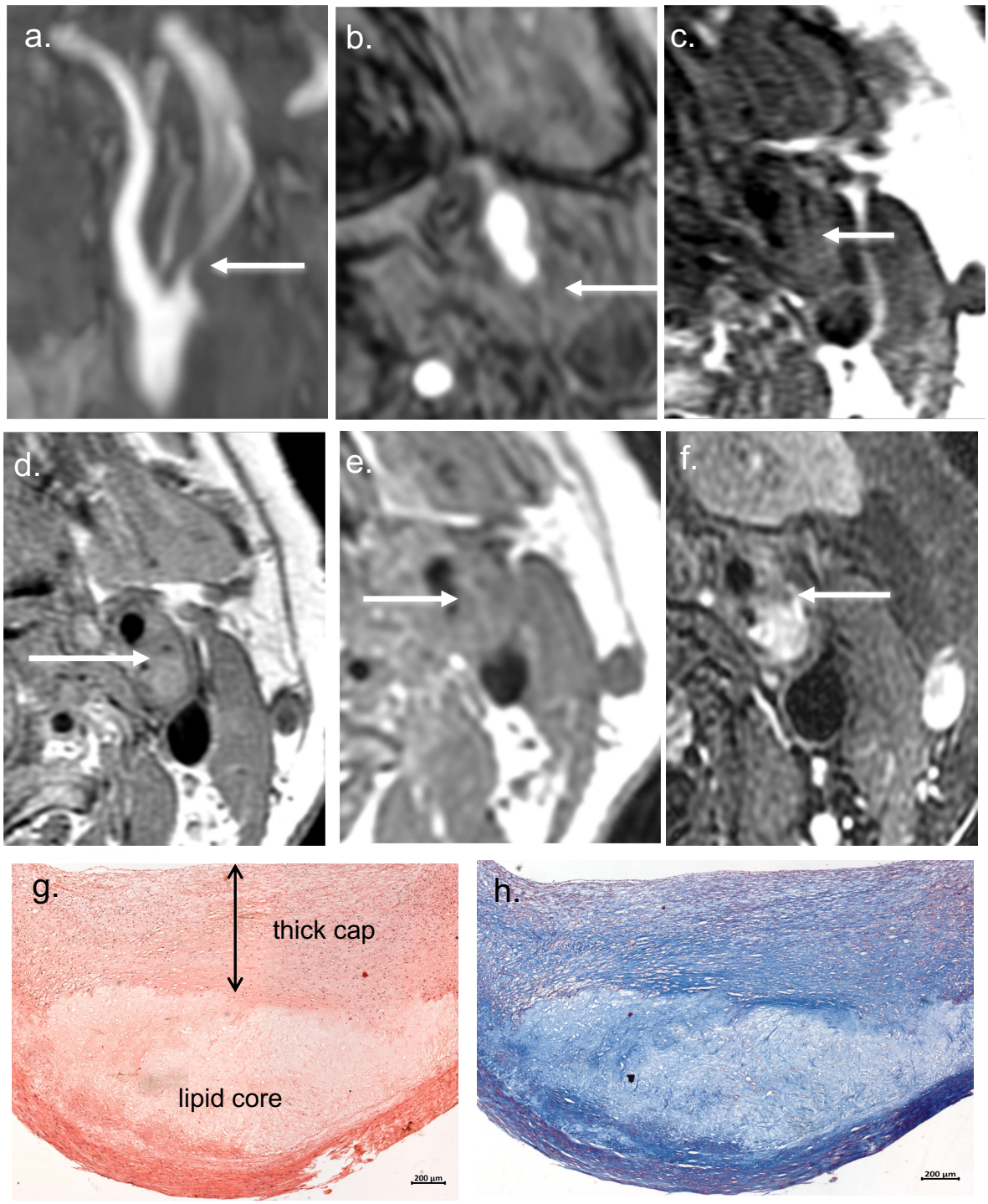
ILLUSTRATIVE CASES



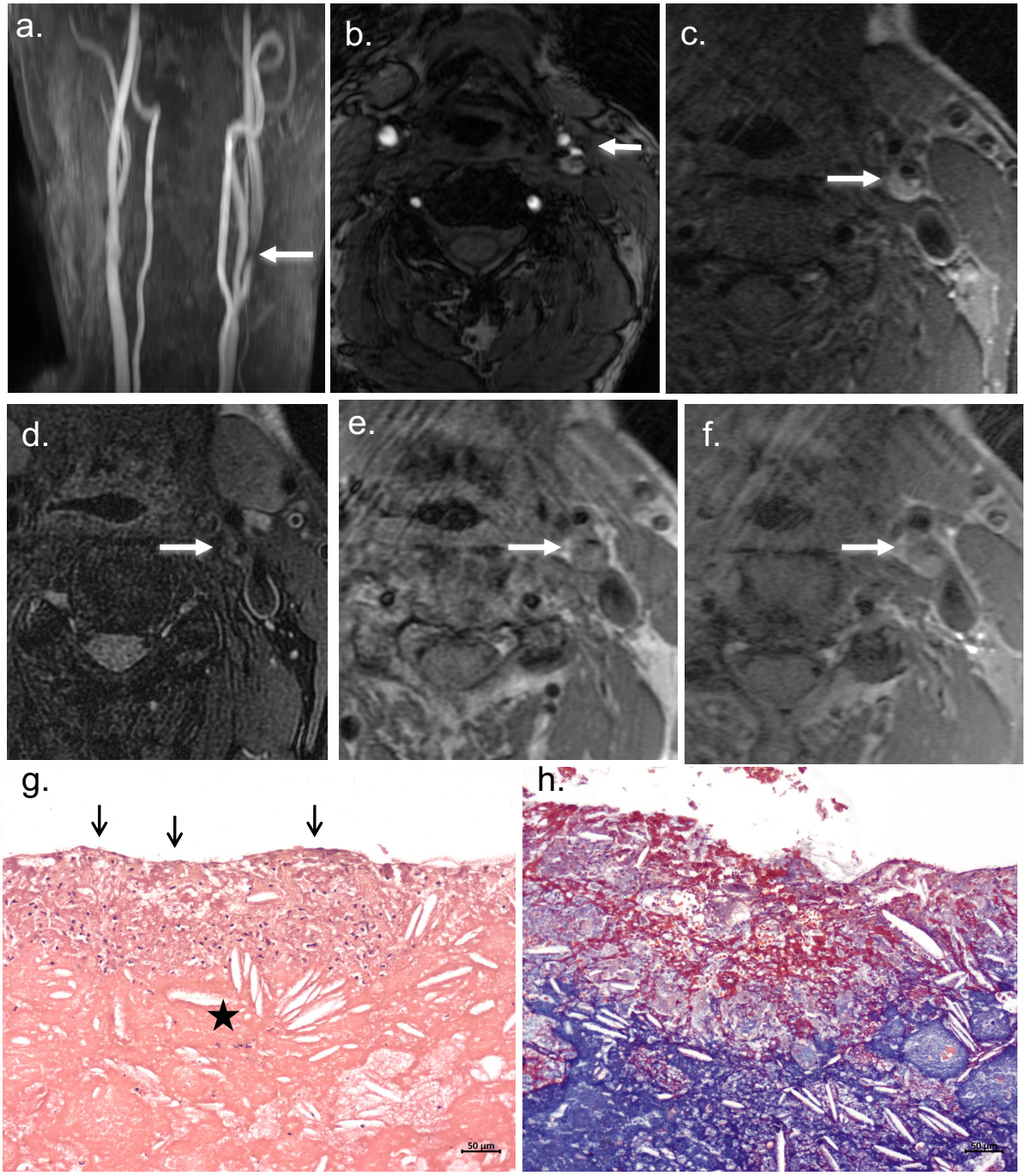
Case 1 : Carotid MR images of a 72 year old female presented with acute onset right hemiparesis and NIHSS of 6. Carotid angiogram VRT image (a.) showing 80% stenosis of left proximal ICA. TOF images (b. & c.)showing eccentric hyperintense plaque involving the postero-lateral wall of left ICA. Axial T1 MR (d.) shows hyperintense plaque. Axial T2 (e.) and T2FS (f.) show predominantly hyperintense plaque. Histopathology shows Intraplaque hemorrhage with ruptured cap. Several RBCs (g., thin arrows) in lipid core admixed with cholesterol clefts and the two ends of the ruptured fibrous cap (g & h, thick arrows) with adherent fibrin thrombus (g, arrow heads).



Case 2 : Carotid MR images of a 66 year old male, chronic smoker, presented with acute onset left hemiparesis. MR TOF angiogram(a.) showing 60% stenosis of right proximal ICA. Axial T1 and T1FS MR (b. & c.) show hyperintense plaque. Axial T2FS (d.) and PD(e.) show predominantly hyperintense plaque. Axial T1 post contrast image (f.) shows surface defect. Histopathology shows ruptured cap. Fibrin thrombus (g., arrows) between the two edges of the ruptured cap (h., arrowheads).



Case 3 : Carotid MR images of a 60 year old male, presented with right upper limb weakness and facial deviation, NIHSS of 7. MR TOF angiogram oblique(a.) and axial (b.) show 80 % stenosis in left proximal ICA, just distal to bifurcation. Axial T1 (c.) shows eccentric hyperintense plaque. Axial PD (d.) and T2(e.) show predominantly hyperintense plaque (PD signal > T2 signal). Axial T2FS image (f.) shows hyperintense plaque with hypointense core. Histopathology shows Plaque with central lipid core and thick fibrous cap (g, h).



Case 4 : Carotid MR images of a 66 year old male with diabetes mellitus, presented with acute onset numbness of right upper and lower limb. MR TOF angiogram (a. & b.) show 60% stenosis with surface ulceration in left proximal ICA. Axial T1 (c.) shows eccentric hyperintense plaque. Axial T2FS (d.) and PD(e.) show predominantly hyperintense plaque). Axial T1 Post contrast image (f.) shows enhancement. Histopathology shows probably ruptured plaque, Site of rupture not clear. Fibrin thrombus on the surface (g, arrows) in direct contact with underlying lipid core with cholesterol clefts (h).

ANNEXURES

Curriculum vitae

Last Name – J	First Name - AKASH	Middle Name –
Date of Birth (dd/mm/yy) 17/12/1992		Sex MALE
Study Site AfLiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) PRINCIPAL INVESTIGATOR AT SCTIMST		

Professional Mailing Address (Include Institution name)	Study Site Address (Include Institution name)
AKASH J. DEPT. OF NEUROLOGY SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA, INDIA - 695011	DEPT. OF NEUROLOGY SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA, INDIA - 695011
Telephone (OfLice):	Mobile Number: 9743431499
Telephone (Residence):	Email- iamakashj@gmail.com

Academic QualiLications (Most recent qualiLication Lirst)

Degree/CertiLicate	Year	Institution, Country
MD GENERAL MEDICINE	2020	MYSORE MEDICAL COLLEGE AND RESEARCH INSTITUTE, MYSORE
MBBS	2016	KASTURBA MEDICAL COLLEGE, MANIPAL

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration
KARNATAKA STATE MEDICAL COUNCIL REGISTRATION NUMBER- 113107 , YEAR :2015

Current and previous positions (most recent position Lirst)

Month and Year	Title	Institution/Company, Country
JAN 2021	SENIOR RESIDENT	SCTIMST THIRUVANANTHAPURAM, INDIA

Brief summary of relevant research experience: 1)POSTER PRESENTATION KAPICON 2021, BELGAUM : ATYPICAL PRESENTATION OF IgA VASCULITIS (HENOCH SCHOLEIN PURPURA) AS RAYNAUD'S PHENOMENON 2)PAPER PRESENTATION- APICON 2020, AGRA: ELASTOGRAPHY COMPARED TO APRI, FIB-4, AST/ALT RATIO FOR ASSESSMENT OF LIVER FIBROSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS 3)MD THESIS : ELASTOGRAPHY COMPARED TO APRI, FIB-4, AST/ALT RATIO FOR ASSESSMENT OF LIVER FIBROSIS IN NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS	
Current project/s at hand:	
Signature: 	Date:28 -08-2021 Place: THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, THIRUVANANTHAPURAM, KERALA - 695011

COMPREHENSIVE STROKE CARE PROGRAM

PATIENT INFORMATION SHEET

Title of the study:
Diagnostic accuracy of MR carotid plaque imaging compared with histopathology in patients with symptomatic carotid artery stenosis.

Principal Investigator:
Dr. Akash J, Senior Resident, Department of Neurology, SCTIMST

Co-Principal Investigator:
Dr. Sylaja PN, Professor, Department of Neurology, SCTIMST

Sir/ Madam,
We invite you to take part in our study titled *"*Diagnostic accuracy of MR carotid plaque imaging compared with histopathology in patients with symptomatic carotid artery stenosis*"* a prospective study. Before you agree to participate in this research study, it is important that you read and understand this information sheet which will provide you with all the information needed for participation in this study so that you can make a well informed and considered decision about participation. In addition, should you have any questions, the investigator and his team members will be happy to answer them and explain to you more about this research study, the procedure involved and the related issues. You may ask them any questions you may have regarding the study, or ask them to explain any word or information that you don't clearly understand.

Study Overview
You are invited to take part in this study as you have stenosis in one of the major blood vessels (internal carotid artery) supplying the brain which is the cause for your stroke. As part of treatment, a procedure called carotid endarterectomy is planned to prevent future cerebrovascular events. A special MR of the carotid artery in which surgery is planned will give more information of the stenosis of the carotid artery and the risk of stroke. Patients diagnosed with symptomatic carotid artery stenosis and planned for carotid endarterectomy who are admitted in Comprehensive stroke care centre, Department of Neurology, SCTIMST will be included in the study.

Purpose of this study
The purpose of this study is to evaluate the diagnostic accuracy of MR carotid plaque imaging in identifying the high-risk carotid plaque in symptomatic carotid stenosis and correlate with histopathology.

Study Procedures
If you are willing to participate, you will be interviewed and examined by neurologist and the clinical findings will be noted. This shall be planned when you are admitted for carotid endarterectomy surgery. Before the surgery you will have to undergo 3T MR carotid plaque imaging as per standard

protocol which will be done free of cost as a part of the study. The investigators will share the details with you.

Risks and Discomfort

This study involves only a structured interview by neurologist along with 3T MR imaging which will be completed in 30 to 40 minutes time. There is no specific risks associated with the study.

Benefits

Taking part in this research study may not benefit you. However, we do hope that this study will shed light whether the advanced MR imaging modality is as good as histopathological morphology and in future for decision making based on the plaque vulnerability rather than degree of stenosis alone.

Confidentiality

Your privacy is very important to us, and the results of the tests performed on you will be treated as highly confidential, and nobody other than the investigators listed above will be knowing the test results. Your name or any other identifiable details will not be published in any research paper or scientific presentation arising out of the study.

Rights

Your participation in the trial is voluntary. You do not have to take part in this study if you are unwilling and you will not be losing any of your rights as a patient if you choose not to participate. You will also be at the liberty to withdraw from the study at any stage (even after signing this consent form) of the study in case you want to withdraw.

Contact Information

5. When you read this information, your treating doctor will be available to discuss and answer any questions you may have. If you have any queries, please contact:

Dr Akash J
Senior Resident, Department of Neurology,
Sree Chitra Tirunal Institute for Medical Sciences and Technology
Tel: +91 9743431499, Email: akashj@sctimst.ac.in

- If you have any questions, concerns or complaints about the research please contact:

Dr. Srinivas G
Member Secretary, Institutional Ethics Committee,
Sree Chitra Tirunal Institute for Medical Sciences and Technology
Tel: 0471- 2524689, Email: iec.mem.sec@sctimst.ac.in

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി, തിരുവനന്തപുരം, കേരളം - 695011
മസ്തിഷ്ക്കാഘാത പരിചരണത്തിനായുള്ള സമഗ്ര പരിപാടി

രോഗിക്കുള്ള കാര്യവിവരണപത്രം

പഠനശീർഷകം:
കരോട്ടിഡ് രക്തക്കുഴൽ സങ്കോചിക്കുന്നതിന്റെ ലക്ഷണങ്ങളുള്ള രോഗികളിൽ കൃത്യമായ രോഗനിർണ്ണയം നടത്തുന്നതിൽ കരോട്ടിഡ് രക്തക്കുഴലിലെ കൊഴുപ്പിന്റെ എം ആർ ഇമേജിംഗും ഹിസ്റ്റോപത്തോളജിയുമായുള്ള താരതമ്യം.

പ്രധാനഗവേഷകൻ:
ഡോ. ആകാശ് ജെ, സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്, SCTIMST

സഹ-പ്രധാനഗവേഷക:
ഡോ. ശൈലജ പി എൻ, പ്രൊഫസർ, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്, SCTIMST

ശ്രീ/ശ്രീമതി,
കരോട്ടിഡ് രക്തക്കുഴൽ സങ്കോചിക്കുന്നതിന്റെ ലക്ഷണങ്ങളുള്ള രോഗികളിൽ കരോട്ടിഡ് രക്തക്കുഴലിലെ കൊഴുപ്പിന്റെ എം ആർ ഇമേജിംഗും ഹിസ്റ്റോപത്തോളജിയും തമ്മിലുള്ള പാരസ്പര്യം എന്ന ഭാവികാലപ്രാപ്യമായ പഠനത്തിൽ പങ്കെടുക്കാൻ താങ്കളെ ഞങ്ങൾ ക്ഷണിക്കുന്നു. താങ്കൾ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുന്നതിനു മുമ്പ്, ഈ പഠനത്തിൽ പങ്കെടുക്കാനാവശ്യമായ വിവരങ്ങൾ നൽകുന്ന കാര്യവിവരണപത്രം വായിക്കുകയും മനസ്സിലാക്കുകയും ചെയ്യേണ്ടുന്നത് കാര്യബോധത്തോടെയും വേണ്ടുന്ന പരിഗണനയോടെയുമുള്ള തീരുമാനമെടുക്കുന്നതിന് പ്രധാനമാണ്. കൂടാതെ താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ, അവയ്ക്കുത്തരം നൽകാനും താങ്കളോട് ഈ ഗവേഷണ പഠനം, ഉള്ളടങ്ങുന്ന നടപടികൾ, ബന്ധപ്പെട്ട പ്രശ്നങ്ങൾ എന്നിവയെപ്പറ്റി കൂടുതൽ വിശദീകരിക്കാനും ഗവേഷകനും സംഘാംഗങ്ങൾക്കും സന്തോഷമേയുള്ളു. ഈ പഠനസംബന്ധമായി താങ്കൾക്ക് ഏത് ചോദ്യവും ചോദിക്കാം, താങ്കൾക്ക് വ്യക്തമായി മനസ്സിലാകാത്ത ഏത് വാക്കിനെപ്പറ്റിയും വിവരത്തെപ്പറ്റിയും വിശദീകരിക്കാനാവശ്യപ്പെടാം.

പഠനത്തെപ്പറ്റിയുള്ള പൊതുവായ അവലോകനം
താങ്കളുടെ തലച്ചോറിലേയ്ക്ക് രക്തം നൽകുന്ന പ്രധാന രക്തക്കുഴലുകൾ (ഇന്റേണൽ കരോട്ടിഡ് ആർട്ടറി) സങ്കോചിച്ചതിനാലാണ് (സ്റ്റെനോസിസ്) താങ്കൾക്ക് മസ്തിഷ്ക്കാഘാതം ഉണ്ടായത് എന്നതിനാലാണ് താങ്കളെ ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ ക്ഷണിക്കുന്നത്. ചികിത്സയുടെ ഭാഗമായി ഭാവിയിലെ സെറിബ്രോവാസ്ക്കുലാർ സംഭവങ്ങൾ തടയാൻ എന്റാർട്ടുറെക്ടമി എന്ന നടപടി ആസൂത്രണം ചെയ്തിരിക്കുന്നു. ശസ്ത്രക്രിയ നടത്താൻ ഉദ്ദേശിക്കുന്ന കരോട്ടിഡ് രക്തക്കുഴലിന്റെ ഒരു പ്രത്യേക എം ആർ നടത്തുന്നത് സങ്കോചത്തെക്കുറിച്ചും മസ്തിഷ്ക്കാഘാതത്തിന്റെ അപായ സാദ്ധ്യതയെക്കുറിച്ചും കൂടുതൽ വിവരങ്ങൾ നൽകും. SCTIMST ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റിലെ സമഗ്ര മസ്തിഷ്ക്കാഘാത പരിചരണ കേന്ദ്രത്തിൽ, എന്റാർട്ടുറെക്ടമി ശസ്ത്രക്രിയയ്ക്കായി പ്രവേശിപ്പിച്ചിട്ടുള്ള രോഗികളെ ഈ പഠനത്തിൽ ഉൾപ്പെടുത്തും.

ഈ പഠനത്തിന്റെ ഉദ്ദേശം
കരോട്ടിഡ് രക്തക്കുഴൽ സങ്കോചിക്കുന്നതിന്റെ ലക്ഷണങ്ങളുള്ള രോഗികളിൽ ഉയർന്ന അപായസാദ്ധ്യതയുള്ള കരോട്ടിഡ് കൊഴുപ്പ് കണ്ടെത്തിന്നതിൽ എംആർ കരോട്ടിഡ് പ്ലേക് ഇമേജിംഗിന്റെ രോഗനിർണ്ണയപരമായ കൃത്യത വിലയിരുത്തുകയും അത് ഹിസ്റ്റോപത്തോളജീയുമായി ഏകോപിപ്പിക്കുകയും ചെയ്യുക എന്നതാണ് ഈ പഠനത്തിന്റെ ഉദ്ദേശം.

പഠന സംബന്ധമായ നടപടികൾ
താങ്കൾ പങ്കെടുക്കാൻ സമ്മതിക്കുകയാണെങ്കിൽ, ഒരു ന്യൂറോളജിസ്റ്റ് താങ്കളുമായി അഭിമുഖം നടത്തുകയും കൂടാതെ താങ്കളെ പരിശോധിക്കുകയും ക്ലിനിക്കൽ കണ്ടെത്തലുകൾ രേഖപ്പെടുത്തുകയും ചെയ്യും. കരോട്ടിഡ് എന്റാർട്ടുറെക്ടമി ശസ്ത്രക്രിയയ്ക്കായി താങ്കളെ ആശുപത്രിയിൽ പ്രവേശിപ്പിക്കുമ്പോൾ തന്നെ ഇത് ആസൂത്രണം ചെയ്യുന്നതാണ്. ശസ്ത്രക്രിയയ്ക്കു

മുമ്പ് പഠനത്തിന്റെ ഭാഗമായി സൗജന്യവുമായി താങ്കളെ അംഗീകൃതമായ നടപടിക്രമപ്രകാരമുള്ള 3റ്റി എംആർ കരോട്ടിഡ് പ്ലേക് ഇമേജീംഗിന് വിധേയമാക്കും. ഇത് സൗജന്യമായി ചെയ്യുന്നതാണ്. വിവരങ്ങൾ ഗവേഷകൻ താങ്കളുമായി പങ്കുവെയ്ക്കും.

അപകടസാദ്ധ്യതകളും അസൗകര്യങ്ങളും

ഈ പഠനത്തിൽ ന്യൂറോളജിസ്റ്റ് നടത്തുന്ന സുഘടിതമായ ഒരു അഭിമുഖവും 30-40 മിനിറ്റ് ദൈർഘ്യമുള്ള 3റ്റി എംആർ ഇമേജിംഗുമോ ഉൾപ്പെടുന്നുള്ളു. ഈ പഠനവുമായി ബന്ധപ്പെട്ട് പ്രത്യേകിച്ച് അപകടങ്ങളൊന്നുമില്ല.

നേട്ടങ്ങൾ

ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് താങ്കൾക്ക് നേട്ടമൊന്നുമുണ്ടായേക്കില്ല. എന്നിരുന്നാലും, ആധുനീകമായ എംആർ ഇമേജിംഗ് രീതി- രക്തക്കുഴലിന്റെ സങ്കോചത്തിന്റെ അളവിന്റെ അടിസ്ഥാനത്തിൽ മാത്രമല്ല കൊഴപ്പിന്റെ അപായസാദ്ധ്യതയുടെയും അടിസ്ഥാനത്തിൽ തീരുമാനമെടുക്കാനും ഈ പഠനം സഹായകമായേക്കാമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുക്കുന്നു.

രഹസ്യാത്മകത

താങ്കളുടെ സ്വകാര്യത ഞങ്ങൾക്ക് പ്രധാനമാകയാൽ താങ്കളിൽ നടത്തിയ പരിശോധനകളുടെ ഫലങ്ങൾ വളരെ രഹസ്യമായിരിക്കും, മുകളിൽ പറഞ്ഞ ഗവേഷകർ ഒഴികെ മറ്റാർക്കും പരിശോധനാഭലങ്ങൾ അറിയുകയില്ല. ഈ പഠനഫലമായി ഉണ്ടാകുന്ന ഗവേഷണ പ്രസിദ്ധീകരണത്തിലോ പ്രദർശനത്തിലോ താങ്കളുടെ പേരോ തിരിച്ചറിയാനിടയാക്കുന്ന മറ്റേതെങ്കിലും വിശദാംശങ്ങളോ പ്രസിദ്ധീകരിക്കുകയുമില്ല.

അവകാശങ്ങൾ

ഈ പരീക്ഷണത്തിലെ താങ്കളുടെ പങ്കാളിത്തം സ്വമേധയായാണ്. താങ്കൾക്ക് സമ്മതമില്ലെങ്കിൽ ഈ പഠനത്തിൽ പങ്കെടുക്കേണ്ടതില്ല, പങ്കെടുക്കുന്നില്ലെന്ന് തീരുമാനിച്ചാലും രോഗിയെന്ന നിലയിലുള്ള താങ്കളുടെ അവകാശങ്ങളൊന്നും നഷ്ടപ്പെടില്ല. പഠനത്തിന്റെ ഏത് ഘട്ടത്തിലും (സമ്മതപത്രം ഒപ്പിട്ടശേഷവും) താങ്കൾക്ക് പഠനത്തിൽ നിന്നും പിൻമാറാവുന്നതാണ്.

ബന്ധപ്പെടാനുള്ള വിവരങ്ങൾ

- താങ്കൾ ഈ വിവരങ്ങൾ വായിക്കുമ്പോൾ ചർച്ചചെയ്യാനും താങ്കൾക്കുണ്ടായേക്കാവുന്ന ചോദ്യങ്ങൾക്ക് ഉത്തരങ്ങൾ നൽകാനും താങ്കളെ ചികിത്സിക്കുന്ന ഡോക്ടർ ഉണ്ടാവും. താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക

ഡോ. ആകാശ് ജെ,
സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്,
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി
ഫോൺ +919743431499, ഇമെയിൽ: akashj@sctimst.ac.in

ഗവേഷണത്തെപ്പറ്റി താങ്കൾക്ക് ചോദ്യങ്ങൾ, ഉത്കണ്ഠ അല്ലെങ്കിൽ പരാതി എന്നിവയുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക:

ഡോ. ശ്രീനിവാസ് ജി
മെമ്പർ സെക്രട്ടറി, ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി
ഫോൺ 0471- 2524689, ഇമെയിൽ: iec.mem.sec@sctimst.ac.in

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, THIRUVANANTHAPURAM, KERALA - 695011

COMPREHENSIVE STROKE CARE PROGRAM

INFORMED CONSENT FORM

Title of Study:

Diagnostic accuracy of MR carotid plaque imaging compared with histopathology in patients with symptomatic carotid artery stenosis

Principal Investigator:

Dr. Akash J., Senior Resident, Department of Neurology, SCTIMST

Co-Principal Investigator:

Dr. Sylaja PN., Professor, Department of Neurology, SCTIMST

Please tick the following points:

6.	I agree to participate as a participant in the study described in the Participant Information Sheet attached to this form.	[ ]
•	I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the information sheet has been explained to me to my satisfaction.	[ ]
(iii)	Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation, and I have received satisfactory answers.	[ ]
(iv)	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
(v)	I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.	[ ]

(vi)	I understand that if I have any questions relating to my participation in this research, I may contact my doctor, who will be happy to answer them.	[ ]
(vii)	I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet attached to this form	[ ]

_____
Name of Participant

_____ _____ _____
Signature of Participant Date Time

_____
Name of Caretaker or Next of Kin
(If patient not directly consented)

_____
Relationship with the patient

_____ _____ _____
Signature of Caretaker or Next of Kin Date Time

_____
Name of Witness

_____ _____ _____
Signature of Witness Date Time

_____
Name of Person conducting Informed Consent discussion

_____ _____ _____

Signature of Person conducting Informed Consent discussion Date Time

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി, തിരുവനന്തപുരം, കേരളം – 695011

മസ്തിഷ്ക്കാഘാത പരിചരണത്തിനായുള്ള സമഗ്ര പരിപാടി

കാര്യബോധത്തോടെയുള്ള സമ്മതപത്രം

പഠനശീർഷകം:

കരോട്ടിഡ് രക്തക്കുഴൽ സങ്കോചിക്കുന്നതിന്റെ ലക്ഷണങ്ങളുള്ള രോഗികളിൽ കൃത്യമായ രോഗനിർണ്ണയം നടത്തുന്നതിൽ കരോട്ടിഡ് രക്തക്കുഴലിലെ കൊഴുപ്പിന്റെ എം ആർ ഇമേജിംഗും ഹിസ്റ്റോപത്തോളജിയുമായുള്ള താരതമ്യം.

പ്രധാനഗവേഷകൻ:

ഡോ. ആകാശ് ജെ, സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്, SCTIMST

സഹ-പ്രധാനഗവേഷക:

ഡോ. ശൈലജ പി എൻ, പ്രൊഫസർ, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്, SCTIMST

(താഴെപ്പറയുന്നവയിൽ ദയവായി ടിക് ചെയ്യുക)

(i)	ഈ പത്രികയോടൊപ്പമുള്ള, പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രത്തിൽ വിശദീകരിക്കുന്ന പഠനത്തിൽ പങ്കെടുക്കാൻ ഞാൻ സമ്മതിക്കുന്നു.	[ ]
(ii)	എന്നെ എന്തുകൊണ്ട് തിരഞ്ഞെടുത്തു, പഠനത്തിന്റെ ഉദ്ദേശം, സ്വഭാവം, പരിശോധനയിൽ ഉണ്ടാവാനിടയുള്ള അപായങ്ങൾ എന്നിവ വിവരിക്കുന്ന പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രം വായിച്ചതായും എന്റെ തൃപ്തിയ്ക്കനുസരിച്ച് വിശദീകരിച്ചുതന്നതായും ഞാൻ സമ്മതിക്കുന്നു.	[ ]
(iii)	സമ്മതപത്രത്തിൽ ഒപ്പു വയ്ക്കുന്നതിനുമുമ്പ്, ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് ശാരീരികവും മാനസികവുമായ എന്തെങ്കിലും ഹാനി എനിക്ക് ഉണ്ടാകാൻ സാദ്ധ്യതയുണ്ടോ എന്നതുമായി ബന്ധപ്പെട്ട ചോദ്യങ്ങൾ ചോദിക്കാൻ എനിക്ക് അവസരം ഉണ്ടാവുകയും തൃപ്തികരമായ മറുപടി ലഭിക്കുകയും ചെയ്തു	[ ]
(iv)	എന്റെ പങ്കാളിത്തം സ്വമേധയായാണെന്നും, കാരണമൊന്നും നൽകാതെയും എന്റെ വൈദ്യപരിചരണത്തെ ബാധിക്കാതെയും ഏതു സമയത്തും എനിക്ക് പിൻമാറാൻ സ്വാതന്ത്ര്യമുണ്ടെന്നും മനസ്സിലാക്കുന്നു.	[ ]
(v)	പഠനഫലമായി ശേഖരിച്ച വിവരങ്ങൾ പ്രസിദ്ധീകരിക്കുമ്പോൾ എന്നെ തിരിച്ചറിയാനിടയാകുന്നതൊന്നും വെളിപ്പെടുത്തുകയില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു.	[ ]
(vi)	ഗവേഷണത്തിൽ പങ്കെടുക്കുന്നതുമായി ബന്ധപ്പെട്ട് എനിക്ക് ചോദ്യങ്ങളുണ്ടെങ്കിൽ എനിക്ക് ഡോക്ടറെ ബന്ധപ്പെടാമെന്നും ഉത്തരം തരുന്നതിൽ അദ്ദേഹത്തിന് സന്തോഷമേയുള്ളെന്നും ഞാൻ മനസ്സിലാക്കുന്നു.	[ ]
(vii)	ഈ പത്രികയോടൊപ്പം നൽകിയിട്ടുള്ള പങ്കാളികൾക്കുള്ള വിവരണപത്രവും സമ്മതപത്രവും കിട്ടിയതായി ഞാൻ അറിയിക്കുന്നു.	[ ]

പങ്കെടുക്കുന്നയാളുടെ പേര്

പങ്കെടുക്കുന്നയാളുടെ ഒപ്പ് തീയതി സമയം

പരിചരിക്കുന്നയാളുടെ അല്ലെങ്കിൽ അടുത്തബന്ധുവിന്റെ പേര്
(രോഗി നേരിട്ടല്ല സമ്മതം തരുന്നതെങ്കിൽ)

രോഗിയുമായുള്ള ബന്ധം

പരിചരിക്കുന്നയാളുടെ അല്ലെങ്കിൽ അടുത്തബന്ധുവിന്റെ ഒപ്പ് തീയതി സമയം

സാക്ഷിയുടെ പേര്

സാക്ഷിയുടെ ഒപ്പ് തീയതി സമയം

സമ്മതപത്രത്തെപ്പറ്റി ചർച്ച ചെയ്തയാളുടെ പേര്

സമ്മതപത്രത്തെപ്പറ്റി ചർച്ച ചെയ്തയാളുടെ ഒപ്പ് തീയതി സമയം

PROFORMA

Sree Chitra Tirunal Institute for Medical Sciences and Technology
Thiruvananthapuram, Kerala-695011

TITLE OF STUDY:

Diagnostic accuracy of MR carotid plaque imaging compared with histopathology in patients with symptomatic carotid artery stenosis

1. Personal Data:

1.1. Age ---------- years

1.2 Sex ---------- 1.Male 2.female

1.3. If outpatient or inpatient ----------If outpatient date seen in OPD----------

1.4. If inpatient, date of admission. ---------- Time ----------

1.5. Date of symptom onset——————————————Time----------

1.6. CEA Side: Right/Left/ Bilateral-

1.7. Date of CEA:

1.8. Date of MR plaque Imaging: Period between MR imaging and CEA:

2. Risk factors:(1=Yes, 2=No)

2.1. Hypertension----------

2.2. Diabetes mellitus--------

2.3. Current smoking---------

2.3a. Ex-Smoker----------Stopped ----------years back

2.3b.Tobacco chewing ----------

2.3c. Alcoholism----------

2.4. Coronary artery disease--------

2.5. Peripheral vascular disease--------

2.6. Hyperlipidemia----------

2.7. History of prior stroke --------Date of ictus----------

2.8. History of prior TIA----------Date of ictus----------

2.9. Patients on treatment ----------

2.9a. If yes, Type of treatment ---------- 1.ASA 2.Plavix 3.Aggrenox 4.Coumadin5.statins

3.Symptoms:(1=Yes, 2=No)

3.1. Visual disturbances ----------1.Amaurosis Fugax 3.Hemianopia 4.Diplopia 5.Blurring of vision 6. None

3.2. Weakness ----------1. Face alone 2.Arm 3.Leg 4.Arm and leg 5. Face arm and leg 6.None

3.3. Speech disturbances ----------1.Aphasia 2.Dysarthria3.Both 4.None

3.4. Vertigo----------

3.5. Ataxia----------

3.6. Confusion----------3.7.a. Loss of consciousness ----------

3.7. Seizures ----------

3.8. Duration of symptoms if TIA ---------- minutes

3.8a. Number of TIAs before CEA----------

4. Clinical Examination:(1=Yes, 2=No)

4.1. Pulse rate---------- (If Regular =1, Atrial fibrillation =2)

4.2. Blood pressure at ER Systolic---------- diastolic --------- (first documented BP)

4.3. Bruit ----------

4.4. Weakness ----------

4.5. Numbness----------

4.6. Cerebellar signs----------

4.7. Aphasia----------

4.8. Dysarthria ----------

4.9. Hemianopia----------

4.10. Hemi-spatial neglect ----------

4.11. NIHSS at admission ----------

4.12. mRS prior to stroke ----------

4.12a.mRS at CEA

4.13. ABCD score in patients with TIA----------

5. Investigations:

5.1. Blood glucose in ER----------

5.2. Serum cholesterol----------

5.3. LDL--------

5.4. HDL----------

5.5. Serum triglycerides----------

5.6. Hb A1C----------

5.7. Homocysteine ----------

5.6. ECG----------1.Normal 2.LVH 3.AF 4.Ischemic changes 5.Not done

5.7. Echo-trans thoracic ----------1.Normal 2.LV dysfunction 3.Mural thrombus 4.Valve disease 5.PFO 6.Infective endocarditis 7.Not done.If valve disease, specify -------

6. Diagnostic imaging

6.1 CT scan ----------1. Normal.2. New infarct 3. Old infarct 4. Small vessel Ischemic changes 5.Not done

6.1a. Infarct pattern----------1. Perforator 2. Territorial 3. Border zone pattern 4. Mixed

If mixed specify the combination……..

6.1b. Arterial Territory ----------1.ACA 2.MCA-complete 3.MCA-Inferior division 4.MCA superior division 5.MCA subcortical 6. Posterior circulation

6.2 CT angiogram

6.2a. CT angiogram neck (Symptomatic vessel) -----1. Normal 2.abnormal 3.not done. Specify ----------

6.2b. CTA Intracranial (Symptomatic vessel) --------1. Normal 2.abnormal 3.not done

6.2c. Location of the plaque----------cervical ICA1. Petrous ICA 2. Cavernous ICA 3. Supraclinoid ICA 4. ACA-A1 5.MCA-M1 6.MCA-M2 7. PCA 8. Basilar artery 9. Intracranial vertebral

6.2d. Percentage of stenosis --------- (Exact percentage)only if more than 50%

6.2e. Collaterals----------1. Absent 2. Less than contralateral side 3. Equal to contralateral side 4. Greater than contralateral side 5. Exuberant

6.2f. Plaque morphology----------1. Ulceration 2. Calcification 3. Dissection

6.3 MRI scan ----------1. DWI negative 2.DWI positive single lesion 3.DWI-Multiple lesions 4. Not done

6.3a. Infarct pattern----------1. Perforator 2. Territorial 3. Border zone pattern 4. Mixed

6.3b. Arterial territory ----------1.ICA 2.ACA 3.MCA-complete 4. MCA-Inferior division 5. MCA superior division 6. MCA subcortical

6.4 MRA neck----------1.normal 2.abnormal 3.Not done**. S**pecify----------

6.5 MRA intracranial----------1.normal 2. Stenotic 4. Occluded 5. Irregular and occluded.

6.5a Percentage of stenosis --------- (Exact percentage)

6.6 MR VWI----------1.normal 2.abnormal

6.6a. Thickening pattern---------- 1. Focal (<0.5cm) 2. Diffuse (>0.5cm)

6.6b. Plaque distribution----------1. Eccentric (<50% wall involvement) 2. Concentric (>50% wall involvement)

6.6c. Contrast enhancement--------1. Present 2. Absent

6.7 DSA---------- 1.Normal 2.Abnormal 3.Not done

Data entry same as CTA

6.9 Carotid plaque imaging…….

Overall quality of images for evaluation 1 / 2 / 3 / 4

6.9a. T1W Hyper / Hypo / Iso

6.9b. T2W Hyper / Hypo / Iso

6.9c. PD Hyper / Hypo / Iso

6.9d. TOF MRA

6.9e. DWI Hyper / Not hyper

6.9f. SWI Hypointense areas present/ Not present

6.9g. Plaque Vulnerable/ Not vulnerable

6.9h. Degree of stenosis in MR

6.9j. Thickness of fibrous cap: Not measurable / Measurable If so thickness=

6.9k. Ulceration: Present/ absent

7. Histopathology finding

7.1a Calcification Present / Absent

7.1b Fibrous cap Intact / Ruptured.

7.1c IPH Present / Absent

7.1d Lipid Necrotic core Present / Absent

7. 2: Conventional AHA Classification

7. Type I: Initial lesion with foam cells

8. Type II: Fatty streak with multiple foam cell layers

9. Type III: Preatheroma with extracellular lipid pools

10. Type IV: Atheroma with confluent extracellular lipid core

11. Type V: Fibroatheroma

12. Type VI: Complex plaque with haemorrhage or thrombus

13. Type VII: Calcified plaque

8. Treatment at discharge:(1=Yes, 2= No)

8.1. Aspirin----------

8.2. Clopidogrel----------

8.3. Aggrenox(Aspirin + Dipyridamole)----------

8.4. Statins ----------dose 40/80mg

8.5. Anti-diabetics ----------

8.6. Antihypertensive ----------

9. Outcome at discharge:

Date of CEA

Any periprocedural stroke -Yes / NO

Any periprocedural TIA Yes/ No

Any other vascular events Yes/ No

9.5. If stroke arterial territory -----1. ICA 2.MCA-M1 3.MCA-M2.4.ACA

9.6. NIHSS at discharge----------

9.7.mRS at discharge----------

9.8. If died, cause of death----------1.Vascular 2.Non vascular. Specify----------

10. Three month outcome:

10.1. Outcome at 3 month -------1.Normal 2.Ischaemic stroke3.Haemorrhagic stroke 4.MI 5.CCF 6. Recurrent TIA 7. Death

10.2. Date of event----------

10.3. m RS at 3 months----------

10.4. NIHSS at 3 months----------

10.5. If died, cause of death------1.Vascular 2.Non vascular. Specify ----------

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1774/NOVEMBER/2021 10.01.2022

Dr. Akash J
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Akash,

The Institutional Ethics Committee held on 26th November, 2021, reviewed and discussed your application to conduct the study titled "**DIAGNOSTIC ACCURACY OF MR CAROTID PLAQUE IMAGING COMPARED WITH HISTOPATHOLOGY IN PATIENTS WITH SYMPTOMATIC CAROTID ARTERY STENOSIS**" (IEC/1774).

The following members of the Ethics Committee were present at the meeting held on 26th November, 2021

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
6.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
7.	Dr. Achuth Sankar S. Nair	Ph.D (i.Engineering ii.Music)	Male	Social Scientist	No
8.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
9.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
10.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
11.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST
2. IEC Application Form
3. Project Proposal
4. Declaration Form
5. Informed Consent Form in English and Malayalam
6. Patient Information Sheet in English and Malayalam
7. CV of PI and Co-PIs
8. Proforma
9. Checklist Form
10. SRC Approval Letter

Revised submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST
2. IEC Application Form
3. Project Proposal
4. Declaration Form
5. Informed Consent Form in English and Malayalam
6. Patient Information Sheet in English and Malayalam
7. CV of PI and Co-PIs
8. Proforma
9. Checklist Form
10. Letter addressed to Dr. Sylaja, Professor, Department of Neurology, SCTIMST from Professor Dame Caroline Watkins, Professor of Stroke and Older People's care/ Faculty Director of Research and Enterprise, Faculty of Health and Care, University of Central Lancashire, UK

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

PLAGIARISM ANALYSIS REPORT

PLAGIARISM SCAN REPORT

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