ASSESSMENT OF CAROTID PLAQUE VULNERABILITY USING 3TESLA MAGNETIC RESONANCE IMAGING AND ITS CORRELATION WITH CAROTID ENDARTERECTOMY HISTOPATHOLOGY

THESIS

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CERTIFICATE

This is to certify that the work incorporated in this thesis titled ***"Assessment of Carotid Plaque Vulnerability Using 3 Tesla Magnetic Resonance Imaging and its Correlation with Carotid Endarterectomy Histopathology"*** *for the degree of* ***DM CARDIOVASCULAR IMAGING AND VASCULAR INTERVENTIONAL RADIOLOGY*** *has been carried out by* ***Dr. Ajay Alex*** *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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ASSESSMENT OF CAROTID PLAQUE VULNERABILITY USING 3TESLA MAGNETIC RESONANCE IMAGING AND ITS CORRELATION WITH CAROTID ENDARTERECTOMY HISTOPATHOLOGY

Abstract:

Objectives:

Carotid plaque characteristics is an important determinant for future cerebrovascular events as well as cardiac events. The goal of the study is to assess the ability of non-contrast high field (3 Tesla) MRI to detect the various plaque features which make it unstable.

Methods and Results:

23 patients who were planned for carotid endarterectomy were part of the study and before surgery, underwent carotid plaque MRI in 3T scanner using non-contrast protocol involving T1, T2, TOF and PD with additional DWI sequences. The carotid plaque, post-surgical excision was analyzed histologically and evaluated for plaque characteristics. MRI evaluation revealed strong agreement in the detection of intraplaque hemorrhage (*Kappa value: 0.817*) with a moderate agreement in the detection of lipid necrotic core (*Kappa value: 0.493*) and overall plaque vulnerability (*Kappa value: 0.704*). Only fair agreement was found in the detection of fibrous cap status (*Kappa value: 0.258*). ADC values were also evaluated with a statistically significant difference in mean values between overall vulnerable and non-vulnerable groups. An ADC value of 1.1145 x 10-3 had a sensitivity of 71.4 % and specificity of 81.2 % in differentiating a non-vulnerable from vulnerable plaque.

Conclusion:

This study highlights the role of non-contrast 3T MRI to be able to non-invasively assess carotid plaque vulnerability and hence its utility in carotid stenosis patient management as well as follow up.

INTRODUCTION

INTRODUCTION

Following coronary artery disease and cancer, stroke is the leading cause of death (1). About 80% of all strokes are ischaemic and approximately 25- 50% of these are caused by an unstable carotid artery plaque(2). However, not all plaques become symptomatic and result in a stroke or a transient ischaemic attack (TIA). Treatment of carotid artery stenosis by surgical endarterectomy or stenting can significantly reduce stroke risk. On the other hand, about 3-9% of patients undergoing interventional treatment are expected to suffer stroke or death as a complication from such a treatment, with stenting having a higher risk for major complications than carotid endarterectomy(3). The current selection criteria for intervention are predominantly determined by the grade of stenosis and symptomatology. It is generally accepted to be more aggressive in a high-grade symptomatic carotid stenosis, but invasive interventions in lower-grade stenosis are still a matter of debate. Further, there is growing awareness that stenosis severity alone has limited value in predicting plaque stability and various molecular processes have, independently of the degree of stenosis, shown to be importantly associated with plaque vulnerability. Among the current clinically available imaging modalities, MRI seems the most accurate method to image plaque morphology in carotid artery disease. High-resolution MRI (HR-MRI) can detect differences in morphologic plaque characteristics between symptomatic and asymptomatic carotid plaques. Symptomatic patients were more likely to have a thin fibrous cap(36.5%), intra-plaque hemorrhage(46.5%), a large lipid core(63.8%), and a complex morphology(61.5%) (4). Additionally, these characteristics are said to be an independent predictor of future cardiovascular events. Also, the degree of stenosis is assessed with the use of Magnetic Resonance Imaging (MRI). Thus MRI can be used for identification of patients with vulnerable plaques at risk for embolic events and therefore who are appropriate candidates for surgery. Studies with 3 Tesla (3T) MRI and histology are relatively scarce with no studies published from India to the best of our knowledge. Additionally, the study uses non-contrast sequences for assessment, offering the advantage of performing the same in renal disease or contrast allergy patients. We hope to propose a better delineation of carotid plaque morphology using the 3T MRI once the study is completed and also help in future planning/ follow up of patients with carotid vessel disease.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1. Correlation of plaque vulnerability based on MRI with histopathological correlation

2. To assess the efficacy of Diffusion-Weighted Imaging (DWI) sequence in plaque characterization

3. Comparison of MR carotid stenosis with CT angiography

REVIEW OF LITERATURE

INTRODUCTION

The Global Burden of Disease (GBD) study reported nearly 5.87 million stroke deaths globally in 2010, as compared to 4.66 million in 1990. Thus in the 20 years, there was a 26% increase in stroke-related death worldwide. With the rising proportion of mortality, stroke remains the second leading cause of death worldwide(5)(6). Indian data showed that the crude stroke prevalence in various parts of the country ranged from 44.29 to 559/100,000 persons during the past two decades(7).

Ischemic strokes and transient ischemic attacks (TIAs) are frequently caused by cerebral embolism from an atherothrombotic plaque or thrombosis at the site of plaque rupture(8). Large vessel atherosclerosis is an important cause of stroke, with extracranial internal carotid artery stenosis significantly more common than extracranial internal carotid artery occlusion or intracranial atherosclerotic disease(9). Importantly, for patients with stroke or TIA attributed to severe (> 70%) extracranial internal carotid artery (ICA) stenosis, prompt revascularization with carotid endarterectomy produces a dramatic reduction in recurrent stroke risk(10–12).

Current guidelines for patient selection for CEA is merely dependant on symptoms and degree of stenosis(10). Several studies, however, have suggested the relative importance of plaque characteristics, rather than stenosis, about the future risk for stroke on both the short and the long term(13)(14). Furthermore, local atherosclerotic plaque composition in patients undergoing CEA is an independent predictor of future cardiovascular events(15,16).

Large randomized trials such as the NASCET or the European Carotid Surgery Trial have shown the benefit of CEA for recently symptomatic patients with severe (>70%) stenosis(11,12). There is a lack of clarity concerning the best management strategy in asymptomatic as well as <70% symptomatic patients. The role of CEA in asymptomatic individuals is also still much debated in light of the results of the Asymptomatic Carotid Atherosclerosis Study and the Asymptomatic Carotid Surgery Trial(17,18).

However, patients with lower degrees of stenosis can still develop clinical symptoms, and conversely, some patients with high-grade stenosis never develop symptoms. This suggests that other factors play an additional role, with recent evidence indicating that atheromatous plaque composition is important in detecting which plaques are vulnerable. Therefore, research is ongoing to establish screening tools that better establish the risk to benefit ratio for patients undergoing surgical

intervention. The advent of vessel wall MR imaging and especially the 3T MR scanners the potential role in assessing the risk in having thromboembolic strokes from carotid disease is being widely studied. Additionally, patients with the atheromatous disease often have concomitant problems, such as renal disease, which can make the administration of contrast undesirable in these cases(19). The incidence of gadolinium-associated nephrogenic systemic fibrosis in patients with severe renal disease is approximately 4% with a mortality of up to 31% (20). Implementation of high-resolution magnetic resonance imaging MRI without contrast administration seems one of the most promising techniques to reliably determine the degree of stenosis and plaque characteristics more precisely. This study assessed the agreement between 3 Tesla non-contrast carotid MR imaging and histology for specific carotid plaque characteristics associated with vulnerability in terms of sensitivity and specificity.

MORPHOLOGY OF VULNERABLE PLAQUE

The three main features of vulnerable plaque include Intraplaque hemorrhage, lipid necrotic core, and thin or ruptured fibrous cap(21). (Fig.1) Additionally, neoangiogenesis and inflammatory cell infiltrate in various histological studies have also been correlated with plaque vulnerability.

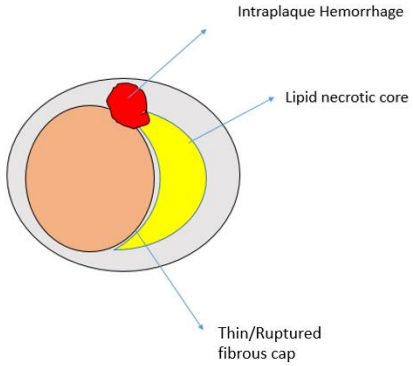

Fig. 1: Diagram showing the three main features of a vulnerable plaque. Additionally increase in inflammatory cells as well as evidence of neo-angiogenesis are also indicative of plaque vulnerability.

COMPARISON OF MRI WITH OTHER MODALITIES

Carotid MRI has many advantages over other imaging techniques. While ultrasound is a widely available method that is commonly used for screening, its spatial and contrast resolution is limited,

reducing its accuracy for evaluating carotid stenosis and plaque components relative to MRI(22). An accurate assessment is also difficult in short neck patients.Computed tomography (CT) has a high spatial resolution, however, its contrast resolution is low compared to MR. Also, it involves ionizing radiation and the imaging of heavily calcified lesions can overestimate the burden of disease. Positron emission tomography (PET) is valuable for the characterization of plaque inflammation but is unable to accurately depict other plaque features and degree of stenosis(23). Digital subtraction angiography reliably depicts the degree of stenosis in two-dimensional planes only, at the cost of its invasiveness, associated radiation exposure, and other procedural risks. Thus of all of the commonly utilized non-invasive clinical imaging modalities, MRI is the most accurate and versatile.

VULNERABILITY ASSESSMENT USING OTHER MODALITIES

Carotid ultrasonography assessment of vulnerability is done based on the echogenicity of the plaque, which depends on its composition(24). A purely hypoechoic plaque is more likely to have acute hemorrhage with a hypoechoic heterogeneous plaque that may have both lipids as well as hemorrhage. Usually, a homogenously hyperechoic plaque would be composed of fibrous tissue and considered stable. Additionally the enhancement within plaque using contrast-enhanced ultrasonography is also believed to indicate possible instability(25).

CT angiographic images depending on density and surface morphology may indicate instability. In one of the studies, a density of <60 HU was used to identify lipid content within the plaque(26). FDG-PET though limited in resolution was also evaluated and found to show increased uptake in plaques with inflammatory infiltrates indicative of vulnerability(27). Other newer techniques of molecular imaging are also being evaluated for the detection of instability within a carotid plaque(21).

1.5 TESLA VERSUS 3 TESLA MR IMAGING

High field MR systems along with dedicated surface coils are required for high-resolution vascular imaging. Several studies comparing T1-, T2-, and proton density-weighted black-blood techniques at 1.5- and 3-T have observed significant improvements in the signal to- noise (SNR) and contrast-to-noise ratios and the overall image quality using the higher field strength system(28). Further improvements to image quality can be achieved through the use of dedicated surface coils by

boosting the SNR and minimizing the propagation of flow artifacts (29). Surface coils require careful positioning(30).

HIGH-RESOLUTION MRI OF VULNERABLE CAROTID ARTERY PLAQUE

Plaque composition can be determined in vivo using a combination of pulse sequences that produce bright-blood and dark-blood images. Several plaque components have a characteristic appearance and can be assessed qualitatively according to established high-resolution MRI classification(31,32). The imaging algorithm that's followed is adapted from the study by Hingwala et al(32), which was done in this institute as well. (Fig.2) The same was described as the basic sequences needed for evaluation by Cai et al and Saam et al as well in their studies(33,34). The basic sequences used include T1, T2, TOF, and PD. Additionally, as part of this study diffusion-weighted MR (DWI) sequence was also studied.

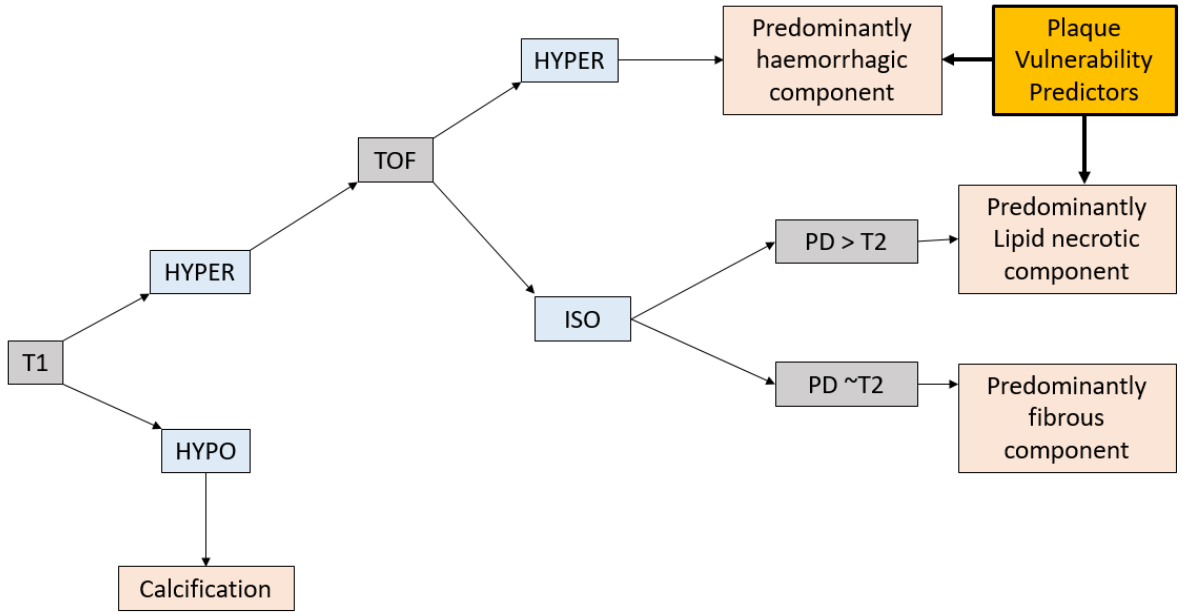

Fig. 2: Algorithm for detecting carotid plaque composition based on MR signals in various sequences. Adapted from study by Hingwala et al (28).

The morphological changes of atherogenesis begin with an outward expansion of the vessel which is demonstrated initially on pathological specimens. Later on, with MRI, the depiction of the artery undergoing compensatory dilation with eccentric remodeling is possible, even before further plaque deposition causes luminal encroachment(35). Identifying plaque components, including the presence or absence of a lipid core, fibrous cap, fibrous tissue components, and calcification can be achieved by varying the image acquisition parameters.

LIPID NECROTIC FOCI

Lipid necrotic core appears hyperintense on T1 image with iso intensity on TOF. The signal intensity in the PD sequence will be higher than in the T2 sequence. The lipid necrotic foci will additionally show DWI hyperintensity with reduced ADC values(36).

INTRA PLAQUE HEMORRHAGE

Intraplaque hemorrhage(IPH) will be hyperintense in both T1 and TOF images. The ability of multi-contrast-weighted MRI to additionally characterize the location of hemorrhage (intraplaque versus juxta luminal) in advanced atherosclerotic lesions has also been established(37). IPH without fibrous cap rupture is not associated with clinical symptoms, whereas juxtaluminal thrombus/hemorrhage indicates an erosion, ulceration, or rupture, each of which is recognized as a marker of vulnerable plaque.

FIBROUS CAP

MRI identification of a ruptured fibrous cap is highly associated with a recent history of TIA or stroke(38). This rupture occurred more likely in plaque with a thin fibrous cap and large lipidic necrotic core. Intact thick fibrous caps showed a uniform dark band adjacent to the lumen on TOF, and a smooth luminal surface on all the images(33,39). A deficient dark band in TOF with surface irregularity, in addition to hyperintensity near the lumen, is indicative of a ruptured fibrous cap in TOF.

FIBROUS PLAQUE

T1 hyperintensity, TOF iso intensity with similar intensities in PD/T2 indicates a non-vulnerable fibrous plaque. As per the AHA histological classification, these come under type VIII plaques which are considered to be stable.

CALCIFICATION

Extracranial carotid artery calcified plaques are significantly less likely to be symptomatic and, thus, may be more stable than non-calcified plaques(40). An inverse relationship between the degree of plaque calcification and macrophage infiltration was found in critical carotid stenosis (41).

Calcifications in MRI will be dark in all sequences. Microcalciifcation detection in MRI may be difficult though detection of the same in CT is considered a predictor of vulnerability(42).

CAROTID STENOSIS

The measurement of percentage diameter carotid stenosis is based on the NASCET criteria. (Fig.3) Carotid stenosis was believed to be overestimated with the MR angiography techniques in previous studies, however, with the advent of high-resolution sequences and black blood techniques, no significant difference in stenosis measurement was noted from CT angiography(43). By using NASCET criteria, a percentage diameter stenosis between 70% and 99% was considered severe.

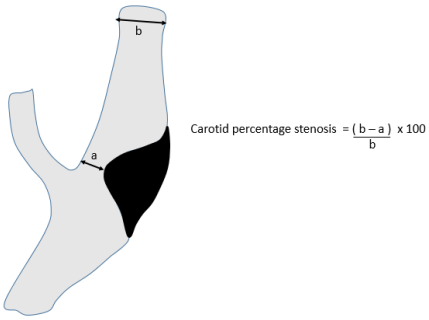

Fig.3: Diagram showing NASCET measurement for carotid stenosis.

When the percentage diameter stenosis measured 50%–69% moderate and less than 50% was considered mild stenosis.

DWI

With the need for non-contrast evaluation for plaque characteristics, DWI was studied for use especially in the detection of the lipid necrotic core. Conventional spin-echo DWI sequences were used in the earlier studies which were mainly used in the analysis of ex vivo plaque specimens of the carotid artery. Clarke et al. reported a multi-sequence examination that included DWI and concluded that incorporating a DWI sequence improved supervised classification algorithms' ability to identify plaque components(44). In 2007, Qiao et al. performed a similar study and generated apparent diffusion coefficient (ADC) maps and reported the range of ADC values in lipid necrotic core and fibrous cap tissue(36).

Due to the previous evidence from ex vivo studies showing that DWI can differentiate LR/NC from other plaque components, studies have sought to apply correctional clinical diffusion-weighted echo-planar imaging sequences to establish if DWI can detect LRNC and fibrous cap in vivo(45). Most of

the above studies were done on a 1.5T MR scanners. Diffusion gradients cause inherent suppression of signal from mobile molecules, whereas more signals are received from stationary molecules, which causes limitations in SNR. Thus using a 3T MRI, is one way to optimize SNR with the resultant issue of artifacts compared to 1.5TMRI. The DW-EPI sequence also has a relatively poor spatial resolution with multi-shot EPI techniques to improve spatial resolution whilst minimizing artifacts and maintaining SNR.

Also, studies have evaluated ADC values with one of the studies showing the mean fibrous cap ADC value was $1.04\times10^{-3}mm^2/s$ ($\pm$SD $0.296\times10^{-3}mm^2/s$) whilst the mean LRNC ADC value was $0.73\times10^{-3}mm^2/s$ ($\pm$SD $0.227\times10^{-3}mm^2/s$)(45). The above was done in a 1.5T scanner. Normal arterial wall assessment in 3T MR in one of the earliest in vivo studies had an ADC value of 1.28×10^{-3} mm^2/s(46). Most of the studies mentioned above have used a b value of 500 for analysis with varying b values also influencing the ADC assessment(47,48). Issues concerning optimal selection of b values are also vital depending on the organ being imaged with lower b values having issues of pseudo diffusion influence as in previous studies(47,49). Also reduction of blood flow signals is achieved, when choosing a b value of 10 instead of 0 for baseline, with the insignificant influence of microvessels within the plaque(48).

SWI

Raman et al. evaluated carotid plaques in vivo and detected reduction of T2* in symptom-causing plaques which were believed to be due to the higher amounts of T2*-shortening forms of iron. In the setting of acute stroke, susceptibility-weighted imaging has been used to demonstrate intra-arterial thrombus(50). The utility of susceptibility imaging has been applied in the assessment of calcification in the femoral artery using a 3D acquisition protocol with high vessel wall contrast with broad coverage (51). It is also sensitive to small amounts of blood components (hemosiderin) and is possible in the future to study both calcifications and hemorrhage. Currently, the assessment of carotid IPH is mainly based on magnetic resonance imaging (MRI) techniques, such as time-of-flight (TOF), magnetization-prepared rapid acquisition with gradient echo (MP-RAGE), and T1-weighted sampling perfection with the application of optimized contrasts using different flip angle evolution (T1-SPACE) sequences. IPH signal intensity on MRI relies on erythrocyte integrity and the oxidation state of hemoglobin(52). Hemoglobin degrades from deoxyhemoglobin to methemoglobin in the acute status,

and later to hemosiderin in the chronic stage. MP-RAGE has been demonstrated to have a high accuracy in carotid IPH detection validated by histology(53). However, a previous study showed that the sensitivity of MP-RAGE was decreased when detecting IPH with a small size or coexisting calcification(54). A recent study has evaluated the QSM sequence for differentiating the hemorrhage from calcification in carotid plaque(55).

HISTOPATHOLOGICAL CLASSIFICATION OF ATHEROSCLEROTIC PLAQUE

The American Heart Association has put forth a classification(Table 1) for the atherosclerotic plaque morphology which was mainly for coronary artery disease, however applicable also for the carotid disease(56).

Table 1:Terms Used to Designate Different Types of Human Atherosclerotic Lesions in Pathology

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-hemorrhage, and/or thrombotic deposit	A complicated lesion, complicated plaque	

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(57).

Best medical therapy involves the use of antiplatelet agents and statins generally in addition to other risk factor modification.

Antiplatelet therapy

The Clopidogrel and Aspirin Regimen for the Reduction of Emboli in the Symptomatic Carotid

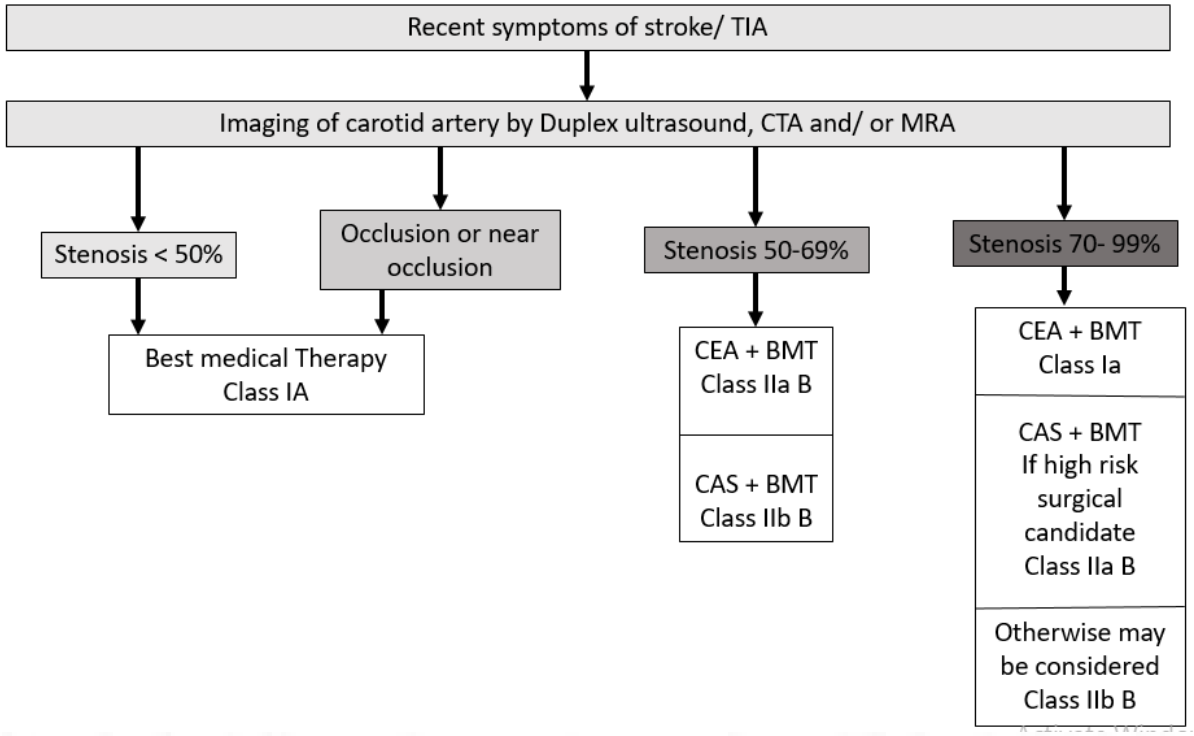

Fig.4: Flow chart showing the evidence based management options in carotid artery stenosis

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(58). 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 microembolic 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(59). 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(60). 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

With the availability of newer advances in imaging, it is essential to reconsider the assessment of vulnerable carotid artery plaques to optimize management options. Accordingly, a new strategy for athero-thrombotic risk must include a combination of systemic markers and high-resolution MRI of components of atherosclerotic plaque. Additionally use of non-contrast MR as an option especially in renal disease patients and also for follow up of patients who are on the best medical therapy, will be the advantages that MR offers. This is all the more important with the US FDA publishing a safety announcement regarding gadolinium contrast agents having the risk of brain deposits on repeated usage. Thus in July 2015, US FDA has stated: “To reduce the potential for gadolinium accumulation, health care professionals should consider limiting gadolinium-based contrast agents use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols.” (61) This risk must now be weighed against the potential radiation hazard

described earlier that limits longitudinal plaque monitoring by CT. This study intends to analyze the use of 3T MR in carotid plaque, especially in the Indian scenario, for the future of better imaging and less invasive follow up of patients.

MATERIALS AND METHODS

MATERIALS AND METHODS

INTRODUCTION

This was a prospective study conducted after obtaining the institutional ethics committee approval from October 2018 to June 2020. Informed written consent was obtained from all the participants who were part of this study.

Consecutive patients with moderate to severe (>50% stenosis) carotid artery stenosis planned for carotid endarterectomy, by the SCTIMST stroke clinic after a multidisciplinary team meeting, were considered for inclusion. These patients underwent magnetic resonance carotid plaque imaging as per the below-stated protocol. The decision regarding the need for carotid endarterectomy was done as per standard guidelines followed in the institution. The patient underwent the surgery in the Department of Vascular Surgery, SCTIMST following the magnetic resonance imaging. For the study, magnetic resonance images were obtained from picture archiving and communication system (PACS), anonymized and stored separately in numbered folders.

These images were analyzed by a reader with 5 years of experience in interpreting diagnostic vascular imaging studies. The parameters were analyzed for the image quality cum diagnostic confidence and graded using a 4-point scale. An image-quality rating from 1 to 4, with 1 being poor and 4 being excellent, was assigned to all MR images before the review. Studies with an overall image quality rating of 1 and 2 were excluded from the study.

The images were independently assessed for the following parameters: signal intensities of carotid plaque (which was compared relative to the signal in sternocleidomastoid on the ipsilateral side of the carotid artery being evaluated.) in various sequences as detailed below. The predominant signal intensity was taken into consideration with the overall assessment of the carotid plaque made as per the algorithm described earlier which was prepared earlier in our institute. Images were assessed on the GE advantage workstation

version 4.6 using the GenIQ application. The same workstation was used for the measurement of the ADC values of the carotid artery plaque at the site of maximum thickness. After data collection, statistical analysis was done to generate inferences.

INCLUSION CRITERIA

- All consecutive patients with significant (>50%) and/or symptomatic carotid artery stenosis in the Stroke clinic who were planned for carotid endarterectomy.

EXCLUSION CRITERIA

- Patients or relatives who declined consent.
- Claustrophobic patients, patients with 3 Tesla incompatible metallic implants, pacemakers, or cochlear implants.

STUDY DESIGN

This was a prospective study involving 27 study subjects. The recruitment of subjects for the prospective study was being done by the principal investigator from 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 or CT angiography. The decision for carotid endarterectomy for patients registered in the Stroke Clinic, SCTIMST was made by a multidisciplinary team involving neurologist, vascular surgeon, neurosurgeon, and interventional radiologist. These patients underwent MR imaging in the Department of IS&IR, SCTIMST before carotid endarterectomy. Following the plaque excision, the specimen was evaluated by the Pathologist for its vulnerability, and a comparison of MR images and histopathological data was done by the investigator.

The study period was from October 2018 to June 2020.

Consent for inclusion in the study was obtained from appropriate persons or guardians. No inclusion of person incompetent to give informed consent, normal/healthy volunteer, Prisoner, student/staff of the institute was done. Clinical information was obtained through patient interviews and supplemented with a chart review.

FLOW CHART OF STUDY DESIGN (Fig.5 and 6)

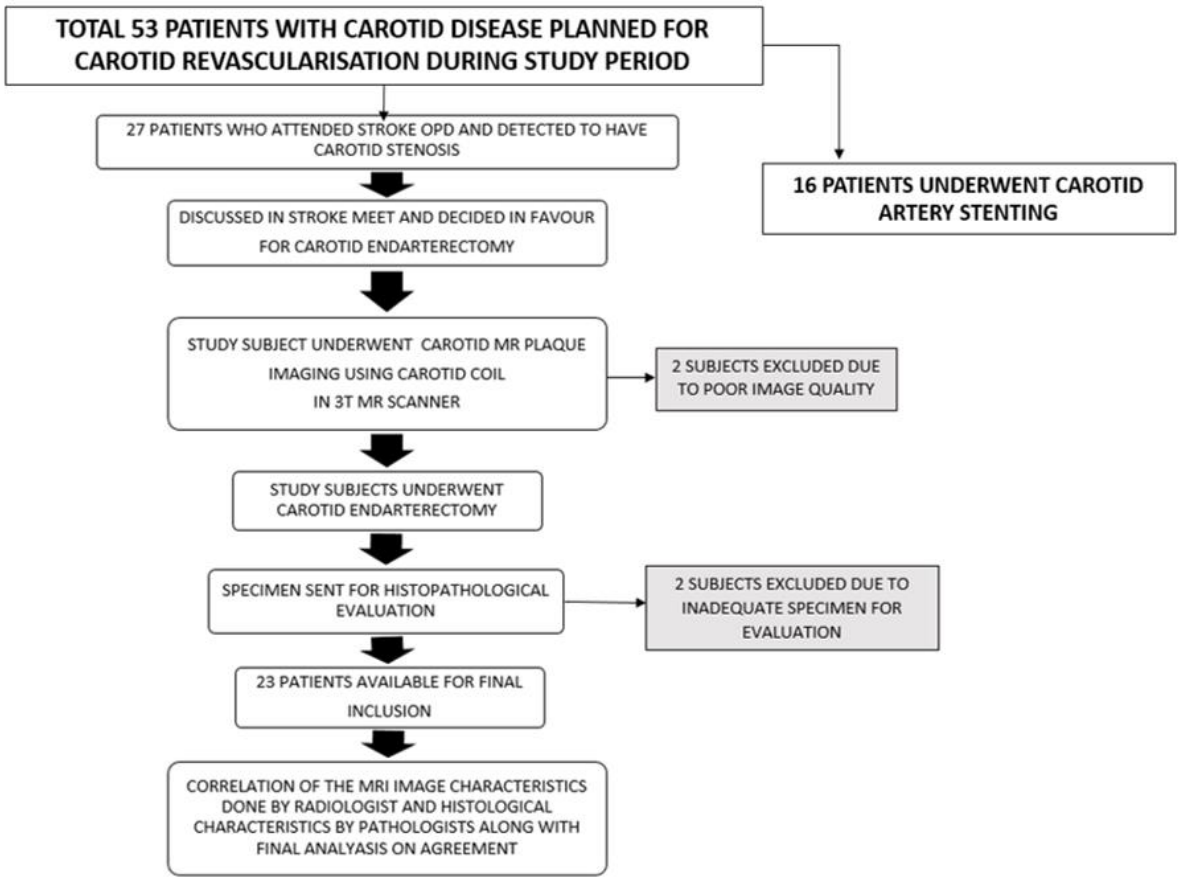

Fig. 5: Flow chart of study design

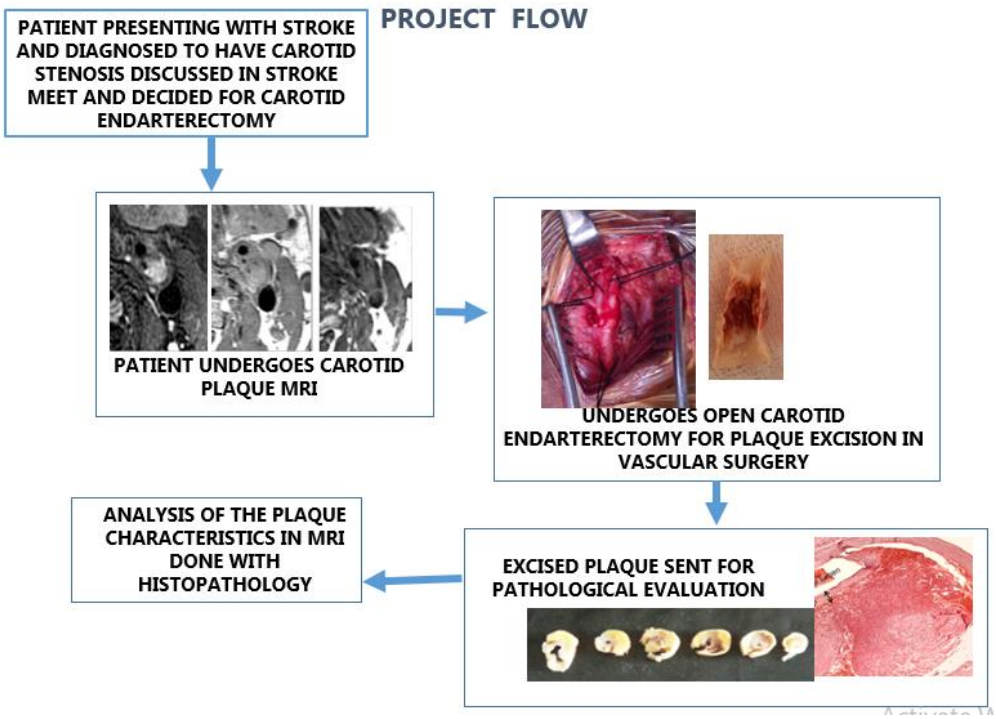

Fig. 6: Various steps involved in the project design

STUDY PROTOCOLS

MRI PROTOCOL

The study subjects underwent Carotid Plaque MR imaging in General Electric Discovery 750E 3.0 Tesla machine using a 6 channel carotid coil. (Fig.8) Before placement of the patient in the MR scanner, the level of the maximum carotid stenosis was marked over the skin using ultrasonography to ensure optimal carotid surface coil position and resultant better signal. (Fig.7) The Magnetic resonance imaging sequences used and parameters are as stated below. (Table 2)

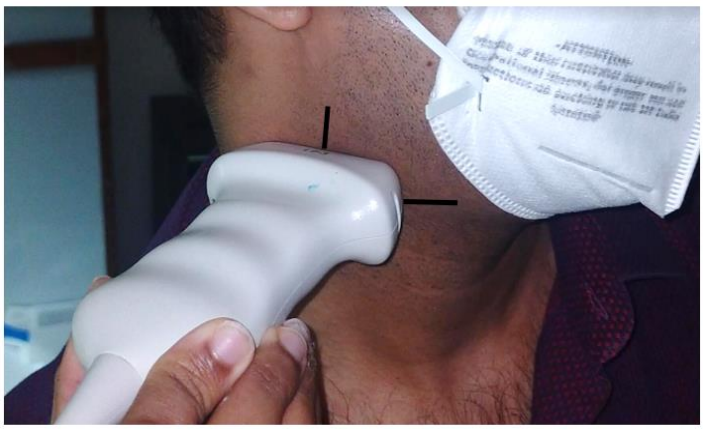

Fig.7: Technique of marking the site of carotid plaque using ultrasonography so as to ensure optimal positioning of the carotid coil

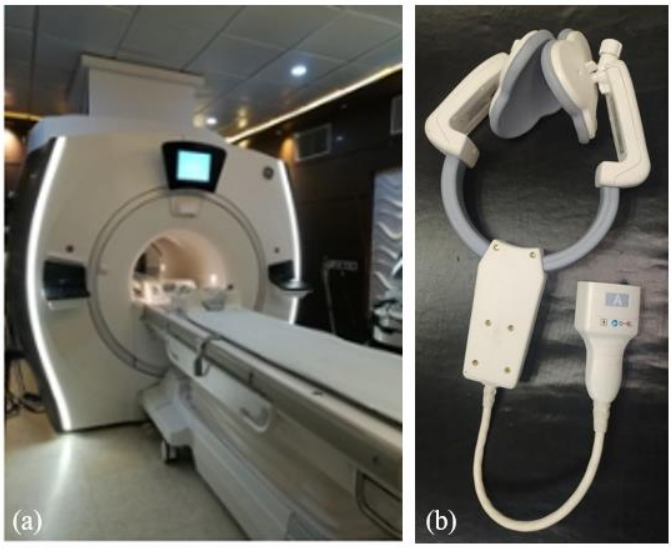

Fig. 8: (a) GE 3 Tesla Discovery scanner used for the study. (b) 6 channel carotid coil used for the study

All images were acquired in the transverse plane except for CUBE sequences which were done in the sagittal plane and were centered to include the carotid bifurcation on the affected

side. The regions of carotid stenosis were identified on rapid-screening TOF MRA, which evaluated the middle 15 cm of the neck.

Table 2: MR Sequence parameters used as part of the study

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

In DWI acquisition, saturation bands were positioned superiorly and inferiorly to suppress signals from in-flowing blood and anteriorly and posteriorly to minimize wrap-around artifact. b values used in the study were 10 and 500. This study used a standard diffusion-weighted echo-planar sequence to provide a degree of robustness against the involuntary patient motion and keep acquisition times clinically acceptable. Additionally, the zero interpolation algorithm(ZIP) was applied in T2, T2 FS, PD, and CUBE T1 sequences.

The MRI images were then retrieved from the PACS and stored in separately numbered folders. The images were analyzed independently using the GE advantage workstation. The software application GenIQ was used for all the evaluation including for diffusion parameter assessment. ADC maps were generated with ROI drawn after correlation with T2

and T2 FS sequences, with regards to the outer and inner limits of the plaque. The mean ADC values were recorded from the ROI, using a b value of 500.

CAROTID ENDARTERECTOMY

The plaque was excised as far as possible in a single piece and transferred without manipulation into a formalin bottle, sealed, and sent for pathological evaluation.

HISTOPATHOLOGICAL EVALUATION OF THE PLAQUE

The endarterectomy specimens were fixed in buffered formalin immediately after surgery. Serial cross-sections were taken from the specimens at 2 mm intervals and processed as per routine protocols in the histopathology laboratory. For all cases, the entire endarterectomy specimen was processed. Haematoxylin and Eosin (H & E), Masson's trichrome (MAT), and elastic van Gieson (EVG) stains were performed on 5μm sections. All the slides were assessed by the pathologist and the histological features were scored using a semi-quantitative method as described by Lovett J K, et al, and indicated in Table 3 (62,63). Inflammation was assessed based on the infiltrate of lymphocytes and histiocytes on H & E sections. The atherosclerotic plaques were also classified as per the American Heart Association (AHA) histological classification of atherosclerosis(56). The minimum and maximum thickness of the atherosclerotic cap was measured on H & E sections using the Zeiss Axio Imager.A2 microscope with Zen software (Carl Zeiss, Germany). A thin cap was defined as a cap thickness of ≤200μm(62,63). Few histological images from our study areas are provided in Fig.9 and 10.

Table 3: Semi-quantitative scoring of various histological parameters

Histological parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hemorrhage	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 hemorrhage or inflammation)	Probably unstable (features of instability, but no rupture: inflammation, thin cap, large lipid core)	Definitely unstable (rupture, thrombus, large hemorrhage, thin inflamed cap)

As part of the analysis, probably and definitely unstable plaques were categorized as being vulnerable and rest were categorized as being stable similar to the criteria followed in imaging studies. Additionally only large lipid necrotic core and intraplaque hemorrhage were considered for analysis as features of instability.

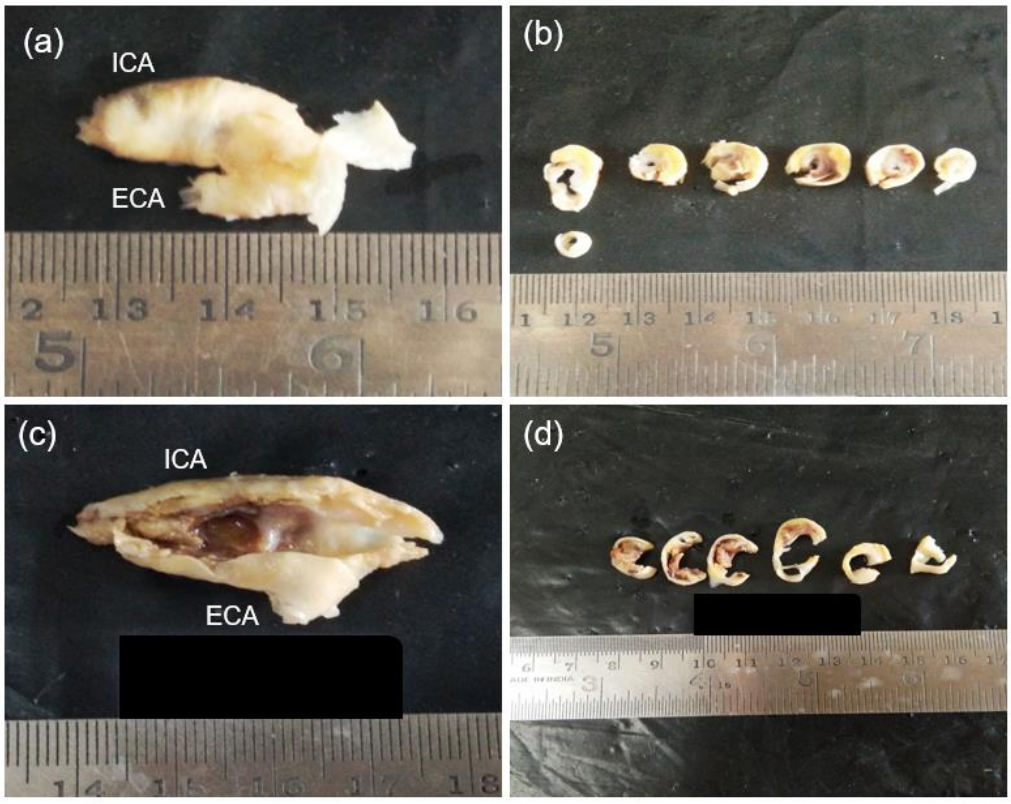

Fig.9: Macroscopic appearance of endarterectomy specimens - intact (a,c) and serial cross-sections (b,d); *ICA: internal carotid artery, ECA: external carotid artery*

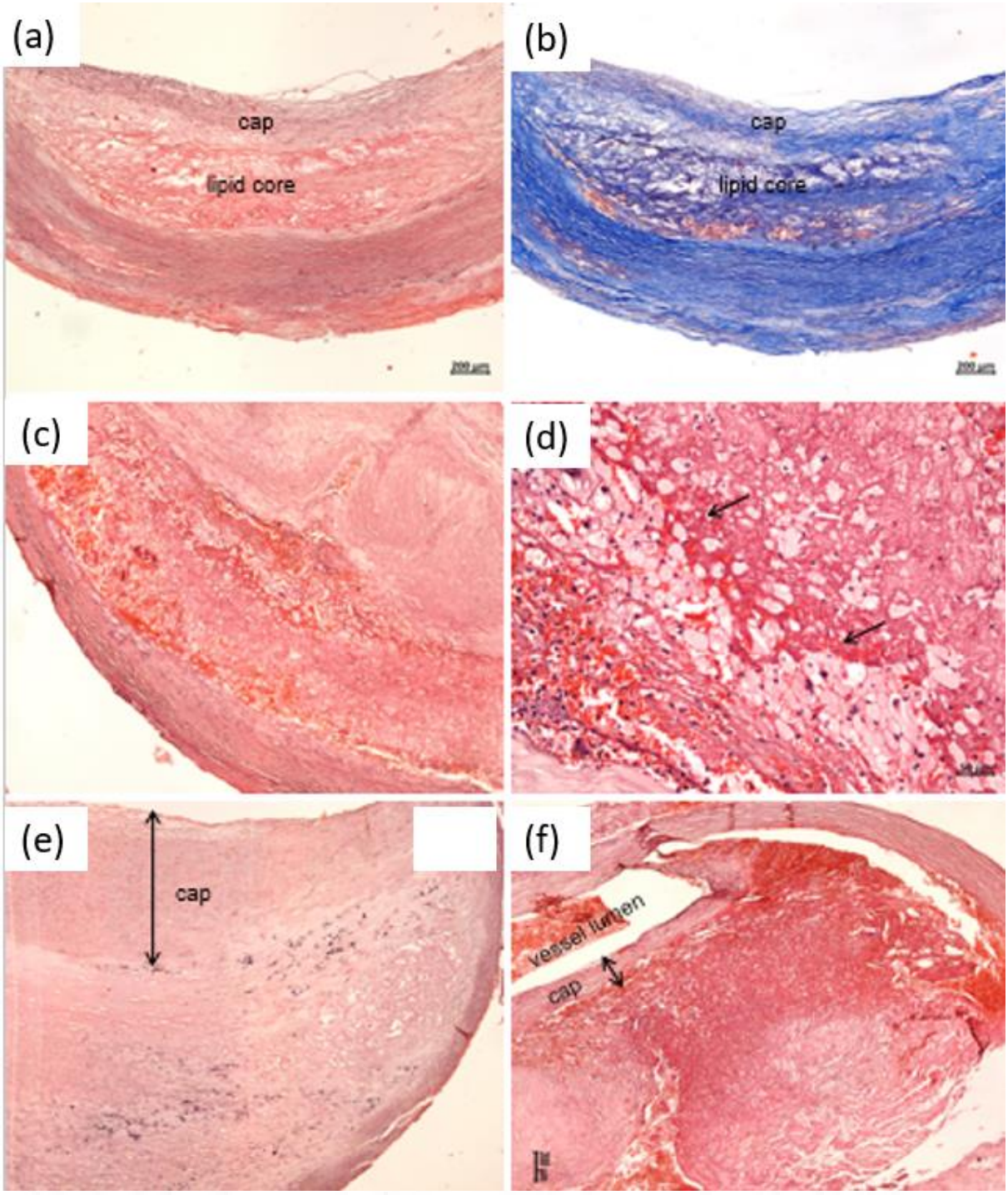

Fig.10: ***Histopathological images showing p*****laque with central lipid core and fibrous cap (*a,b*) containing foam cells in the lipid core (*c,d, arrows*). Plaques with thick (*e*) and thin (*f*) caps.*** *[a, c-f: Haematoxylin and Eosin, b: Masson's trichrome. a-c,e-f: Original magnification 50X, Scale bar 200µm , d: Original magnification 200X, Scale bar 50µm]*

STATISTICAL ANALYSIS

Each patient contributed only 1 set of observations (ie, from only one carotid artery) to the dataset for analysis. Statistical analysis was done using SPSS 23 analysis software. In addition to descriptive statistical tools for basic frequencies of plaque characteristics and patient demographics, a chi-square test was used for assessment of risk factors and plaque characteristics. p-value < 0.01 was defined as being statistically significant. 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. For the assessment of MR and CT quantification of stenosis, the Pearson correlation test was performed. For comparison of mean ADC values between each of the plaque characteristics and overall plaque vulnerability independent sample t-test was performed.

RESULTS

RESULTS

As part of the study, a total of 27 study subjects were imaged. 2 cases were excluded due to the suboptimal image quality in MRI and 2 cases excluded due to the inadequate specimen for histopathological assessment. Thus 92.6% of the cases had adequate image quality for interpretation of plaque characteristics.

DEMOGRAPHICS

65.2% of the subjects were male with all patients aged above 50 years. The minimum age was 50 years and the oldest patient was 74 years with a median age of 66 years in the study population. Also in the study population, only one patient was asymptomatic with all the rest 22 patients having TIA/ stroke history within the last 6 months.

Sex distribution

Table 4: Frequency distribution of sex in the study population

Sex	Frequency	Percent
Male	15	65.2
Female	8	34.8
Total	23	100.0

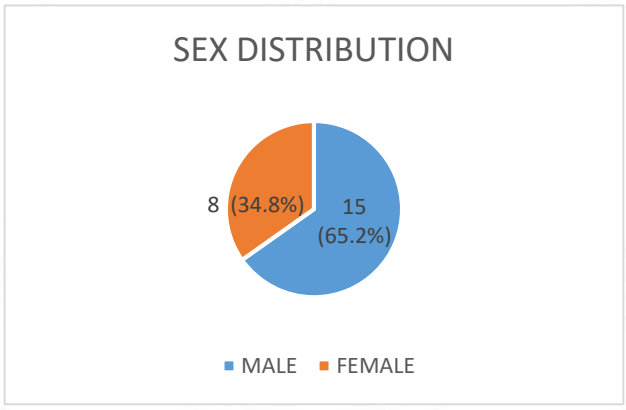

Fig. 11: Frequency distribution of sex in the study population

Age distribution

Table 5: Age distribution in the study population

Age Group	Frequency	Percent
Less than 50yrs	1	4.3
51-60 yrs	2	8.7
61-70 yrs	15	65.2
More than 70 yrs	5	21.7
Total	23	100.0

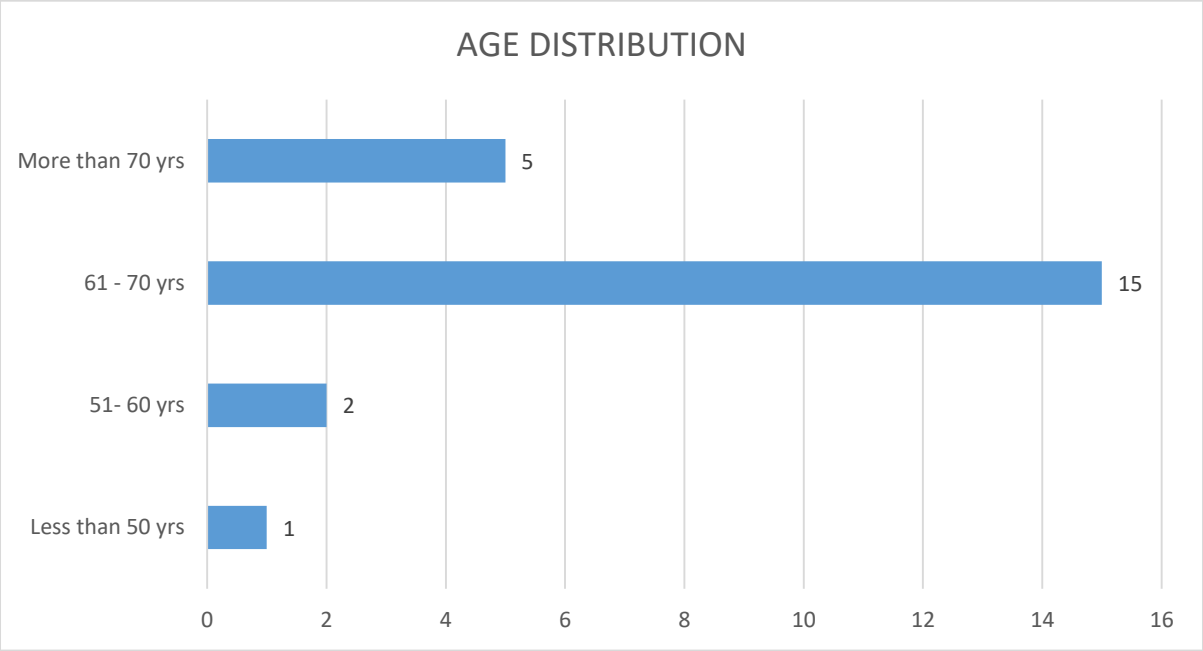

Fig. 12: Age distribution in the study population

RISK FACTORS IN STUDY POPULATION

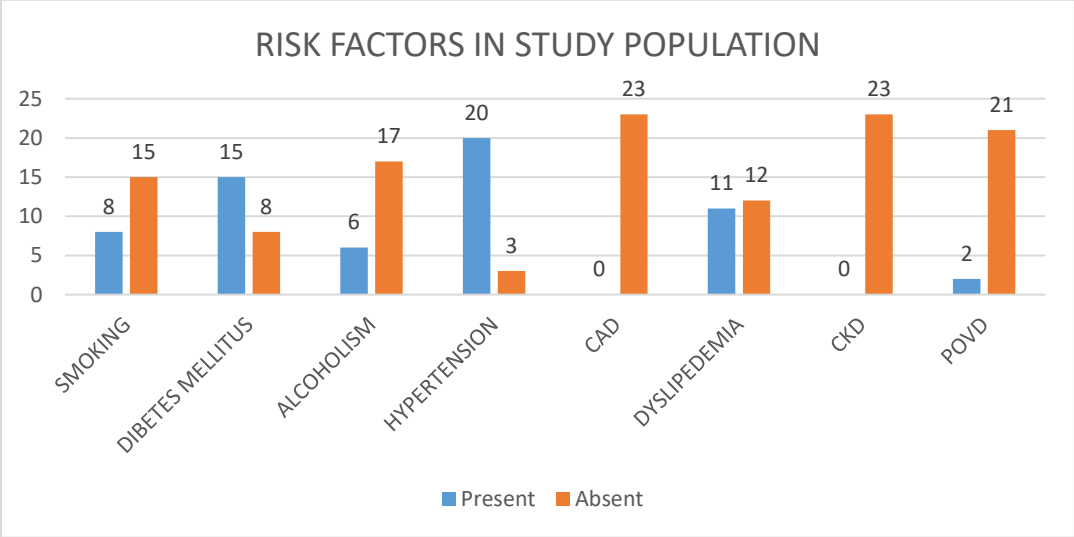

Fig. 13: Risk factors in the study population

Table 6: Risk factors in the study population		
Risk Factor	**Present**	**Absent**
Smoking	8	15
Diabetes Mellitus	15	8
Alcoholism	6	17
Hypertension	20	3
CAD	0	23
Dyslipidaemia	11	12
CKD	0	23
POVD	2	21

Comorbidities of the study population that were analyzed included smoking, alcoholism, diabetes mellitus, hypertension, prior coronary heart disease, dyslipidemia, renal disease, and previous peripheral vascular disease. Hypertension (87%) was the most common risk factor in the study population followed by diabetes (65.2%) and dyslipidemia (47.8%).

SIDE OF CEA SURGERY

A relatively good number of both right (43.5%) and left (56.5%) carotid artery disease was included in this study. None of the cases underwent bilateral endarterectomy during the period of the study.

Table 7: Frequency distribution of ICA endarterectomy

Side	Frequency	Percent
Right	10	43.5
Left	13	56.5
Total	23	100.0

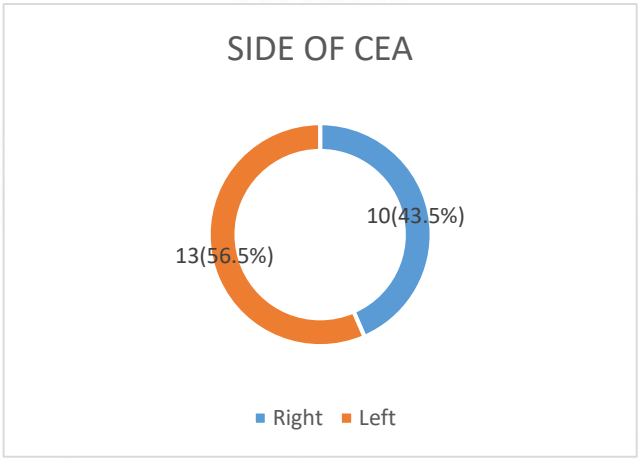

Fig. 14: Frequency distribution of ICA endarterectomy

CAROTID MR IMAGING ANALYSIS

The mean number of days between the study subject having a cerebrovascular event and undergoing carotid plaque MRI was 57 days. The mean number of days between MR evaluation and carotid endarterectomy was 4 days.

CAROTID STENOSIS

The majority (82.6%) of the cases in the study population had severe (>70 %) carotid stenosis. Only 4 patients had stenosis in the region of 50-70%. Minimum stenosis was ~ 57% and the maximum was ~ 87 %.

Table 8: Frequency distribution of the degree of carotid stenosis in the study population		
Degree of Carotid Stenosis	**Frequency**	**Percent**
50-70 % stenosis	4	17.4
More than 70% stenosis	19	82.6
Total	23	100.0

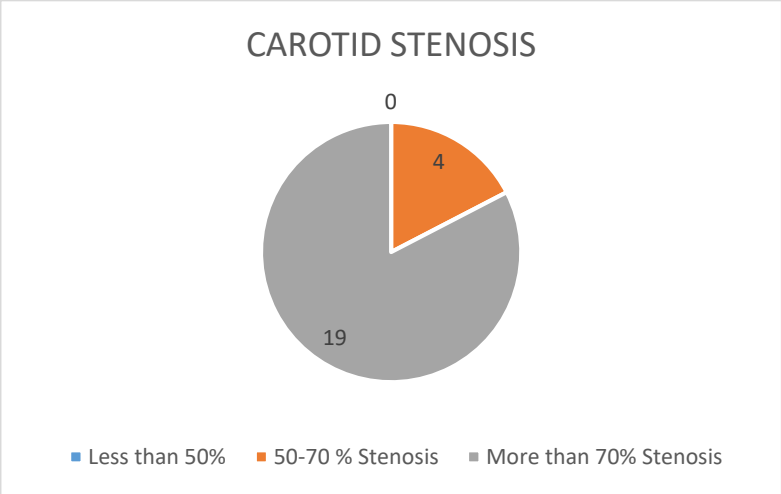

Fig. 15: Frequency distribution of degree of carotid stenosis in the study population

MRI PLAQUE CHARACTERISTICS

Table 9: Frequency distribution of MR plaque characteristics		
MR Plaque Characteristics	**Present**	**Absent**
Intraplaque hemorrhage	9 (39.1%)	14 (60.9%)
Lipid Necrotic Core	9 (39.1%)	14 (60.9%)
Plaque Vulnerability	15 (65.2 %)	8 (34.8%)

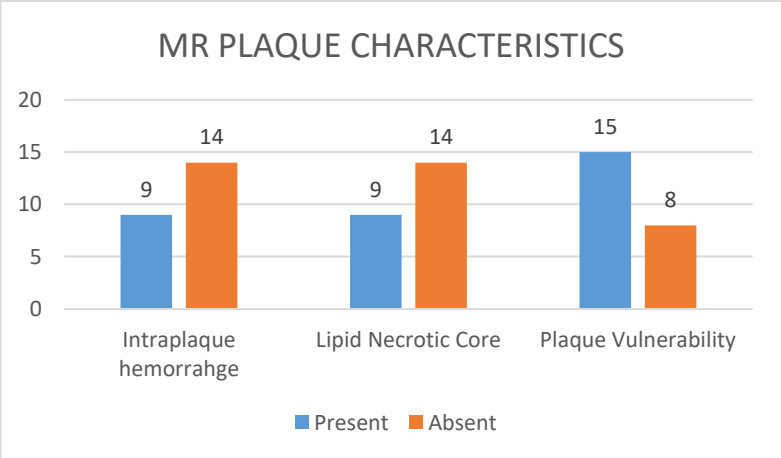

Fig. 16: Frequency distribution of MR plaque characteristics

Approximately 2/3rd of the MR data revealed plaque vulnerability with equal detection of intraplaque hemorrhage as well as lipid necrotic core. Few cases had both LRNC and IPH.

HISTOPATHOLOGICAL PLAQUE CHARACTERISTICS

On histological review, ~ 70 % of the specimens were found to have features suggestive of vulnerability.

Table 9: Frequency distribution of histological plaque characteristics

Histopathological Plaque Characteristics	Present	Absent
Intraplaque hemorrhage	9 (39.1%)	14 (60.9%)
Lipid Necrotic Core	13 (56.5%)	10 (43.5%)
Plaque Vulnerability	16 (69.6 %)	7 (30.4 %)

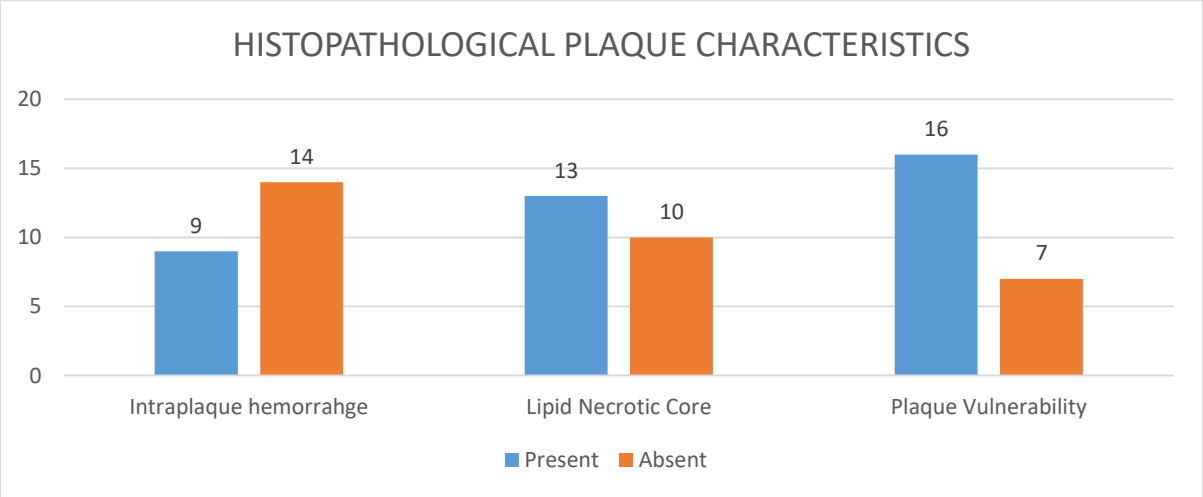

Fig.17: Frequency distribution of histological plaque characteristics

ASSOCIATION OF RISK FACTORS WITH PLAQUE VULNERABILITY

Association of risk factors with plaque vulnerability was assessed among the study population, however, no statistical significance was detected in the present study.

Table 10: Analysis of risk factor associated with plaque vulnerability

Risk Factor		Vulnerable Plaque group	Non-vulnerable Plaque group	*p*-value
Sex	M/F	10 / 6	5/2	0.679
Side of CEA	R/L	5 / 11	5/2	0.74
Smoking	Present/Absent	5 / 11	3/4	0.591
DM	Present/Absent	10 / 6	5/2	0.679
Alcoholism	Present/Absent	4 / 12	2/5	0.858
Hypertension	Present/Absent	13 / 3	7/0	0.219
Dyslipidemia	Present/Absent	7 / 9	4/3	0.554
POVD	Present/Absent	2 / 14	0/7	0.328

- *CAD and CKD could not be assessed.*

LIPID PROFILE WITH PLAQUE VULNERABILITY

Table 11: Analysis of lipid profile parameters with plaque vulnerability					
	Plaque Status	**N**	**Mean**	**Std. Error Mean**	**p-value**
TOTAL CHOLESTEROL	Vulnerable	16	1.2300E2	9.22271	0.502
	Non vulnerable	7	1.1086E2	16.82180	
LDL	Vulnerable	16	71.6875	5.51416	0.515
	Non-vulnerable	7	64.5714	10.38281	
TG	Vulnerable	16	1.1862E2	14.59991	0.241
	Non-vulnerable	7	90.8571	8.38487	
HDL	Vulnerable	16	38.9375	2.36373	0.538
	Non-vulnerable	7	42.1429	5.64602	

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> 0.05).

ASSOCIATION OF NUMBER OF THROMBOEMBOLIC EVENTS AND PLAQUE VULNERABILITY

Table 12: Analysis of prior cerebrovascular events with plaque vulnerability			
NO OF PRIOR CEREBROVASCULAR EVENTS			
	Study Subjects	Mean	Std. Error Mean
Vulnerable	16	2.6875	0.48921
Non vulnerable	7	2.0000	0.75593

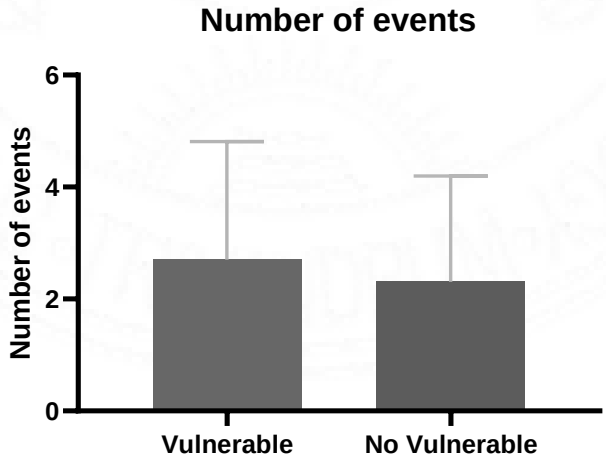

Fig.18: Analysis of prior cerebrovascular events with plaque vulnerability

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, statistically the difference could not be proven with a p-value > 0.05

CORRELATION OF STENOSIS QUANTIFICATION IN CT AND MRI

A good correlation was noted between the MR and CT assessment of stenosis with a Pearson correlation coefficient of 0.748 (*p-value 0.000*).

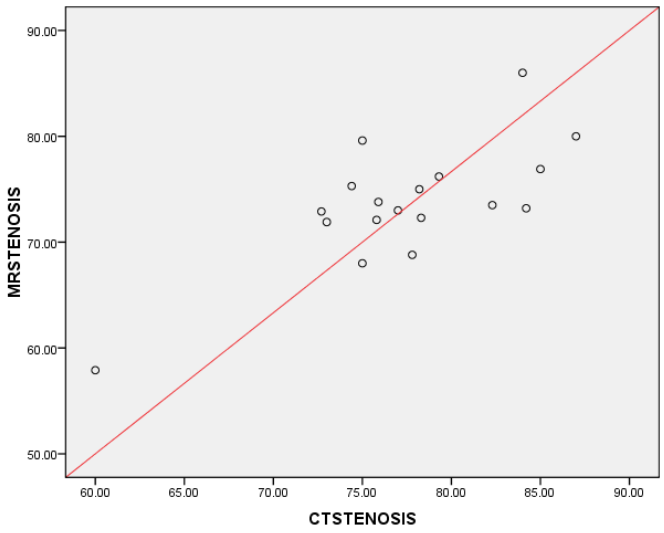

Fig.19: Scatter plot depicting the CT and MR measurements of carotid stenosis in the study population.

There was a good correlation between the stenosis assessment made using CT angiography and MR TOF images. 5 study subjects didn't have CT angiography for assessment in this study.

CORRELATION OF MRI WITH HISTOLOGY

Lipid Necrotic Core

Table 13: Comparison of MR and histological detection of lipid necrotic core in carotid plaque

MR – Lipid Necrotic Core		Histology - Lipid necrotic core		Total
		Present	Absent	
	Present	8	1	9
	Absent	5	9	14
	Total	13	10	23
Kappa value : 0.493 (Moderate agreement); Approx Sig 0.012				

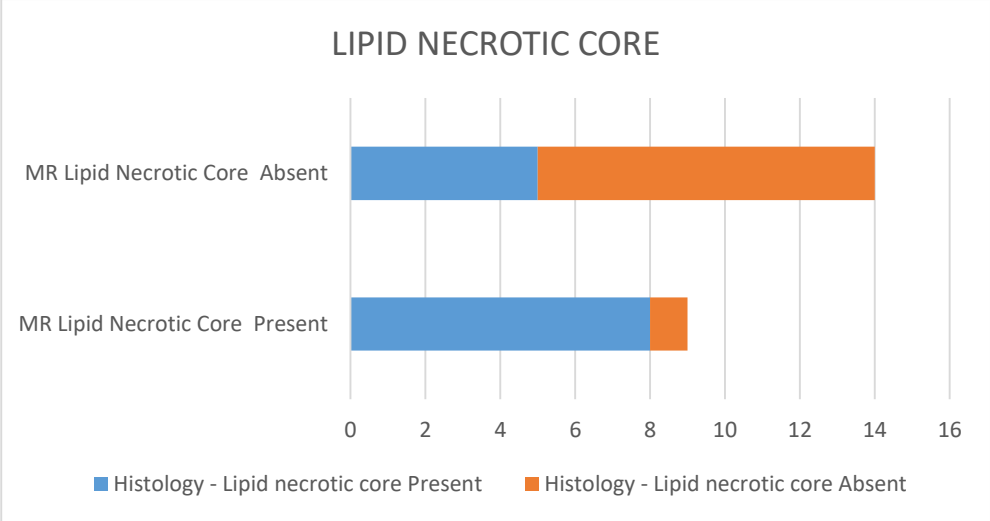

Fig.19: Comparison of MR and histological detection of lipid necrotic core in carotid plaque

Moderate agreement was noted in the detection of lipid necrotic core with MR and histology, with 90% specificity.

Sensitivity	61.5
Specificity	90.0
Positive Predictive Value	88.9
NPV	64.3
Accuracy	73.9
LR+	6.2
LR-	0.43

Intra-plaque Hemorrhage

Table 14: Comparison of MR and histological detection of intraplaque hemorrhage in carotid plaque

MR - Intraplaque Hemorrhage		**Histology – Intraplaque Hemorrhage**		Total
		Present	**Absent**	
	Present	8	1	9
	Absent	1	13	14
	Total	9	14	23
Kappa value : 0.817 (Strong agreement); Approx Sig 0.000				

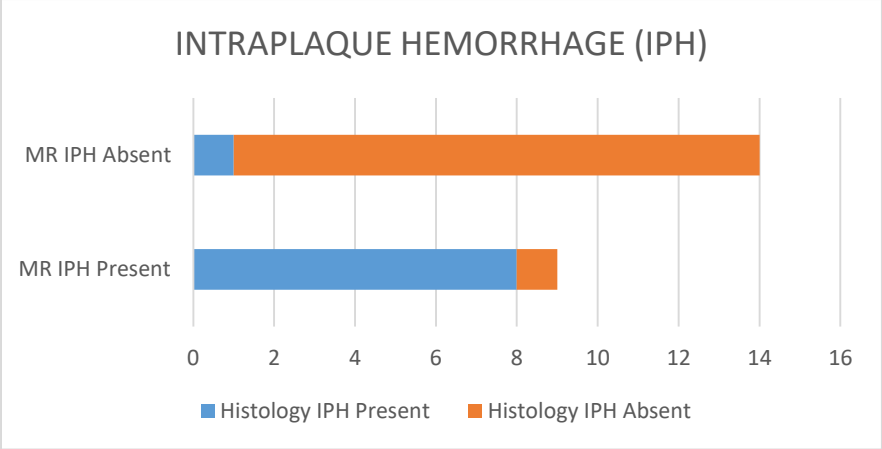

Fig.20: Comparison of MR and histological detection of intraplaque hemorrhage in carotid plaque

Sensitivity	88.9
Specificity	92.9
PPV	88.9
NPV	92.9
Accuracy	91.3
LR+	12.4
LR-	0.12

Intraplaque hemorrhage was the characteristics which was most accurately detected with the present MR protocol with a k value of 0.817.

Fibrous Cap

Table 15: Comparison of MR and histological detection of fibrous cap status in carotid plaque

MR – Fibrous Cap		Histology – Fibrous Cap		Total
		Intact	Ruptured	
	Intact	5	0	5
	Ruptured	10	8	18
	Total	15	8	23
Kappa value : 0.258 (Fair agreement); Approx Sig 0.065				

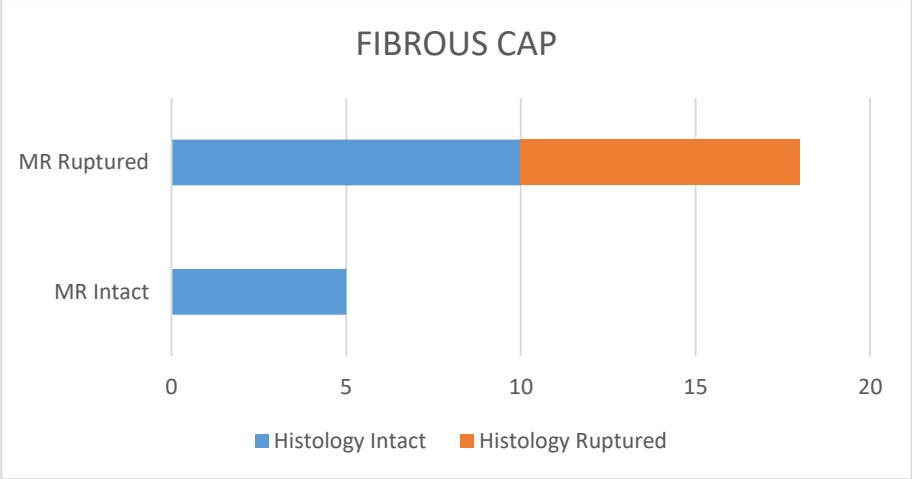

Fig.21: Comparison of MR and histological detection of fibrous cap status in carotid plaque

Sensitivity	33.3
Specificity	100.0
PPV	100.0
NPV	44.4
Accuracy	56.5
LR+	-
LR-	0.67

Though the agreement of fibrous cap status in the present non-contrast protocol was only fair, the specificity was detected to be 100%.

Overall plaque vulnerability

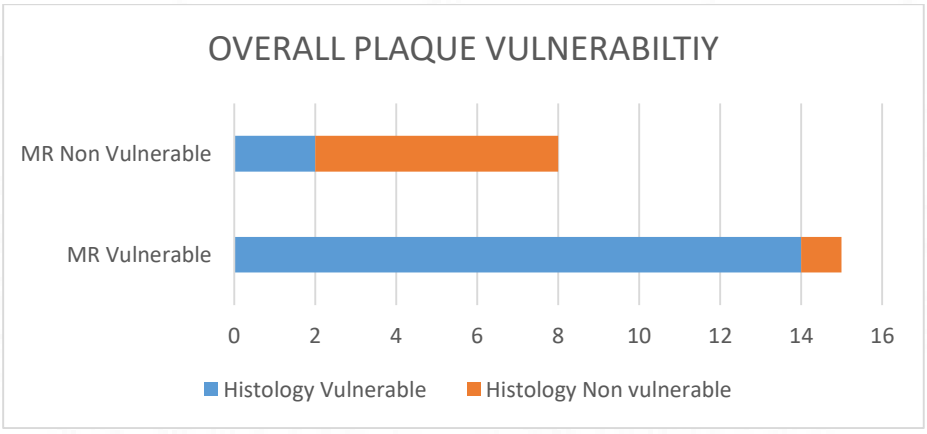

Fig.22: Comparison of MR and histological detection of overall plaque vulnerability in carotid plaque

Table 16: Comparison of MR and histological detection of overall plaque vulnerability in carotid plaque				
MR – Plaque Vulnerability		Histology – Plaque Vulnerability		Total
		Vulnerable	Non-vulnerable	
	Vulnerable	14	1	15
	Non vulnerable	2	6	8
	Total	16	7	23
Kappa value : 0.704 (Moderate agreement); p : 0.001				

Sensitivity	87.50%
Specificity	85.71%
PPV	93.33%
NPV	75.00%
Accuracy	86.96%
LR+	6.12
LR-	0.15

The analysis revealed strong agreement in the detection of intraplaque hemorrhage with a moderate agreement in the detection of the lipid-rich necrotic core and overall plaque vulnerability (kappa 0.704). An only mild agreement was noted in the detection of fibrous cap integrity between MR and histology.

ADC VALUE CORRELATION

Plaque Vulnerability

Table 17: Comparison of ADC mean values between vulnerable and non-vulnerable groups				
		No. of study subjects	Mean ADC value	Std. Error Mean
ADCVALUE	Vulnerable	16	**0.83 x 10^{-3}**	**0.10 x 10^{-3}**
	Non vulnerable	7	**1.7 x 10^{-3}**	**0.29 x 10^{-3}**
P value 0.001 ; 95% CI : 0.405 x10^{-3} - 1.44 x 10^{-3}				

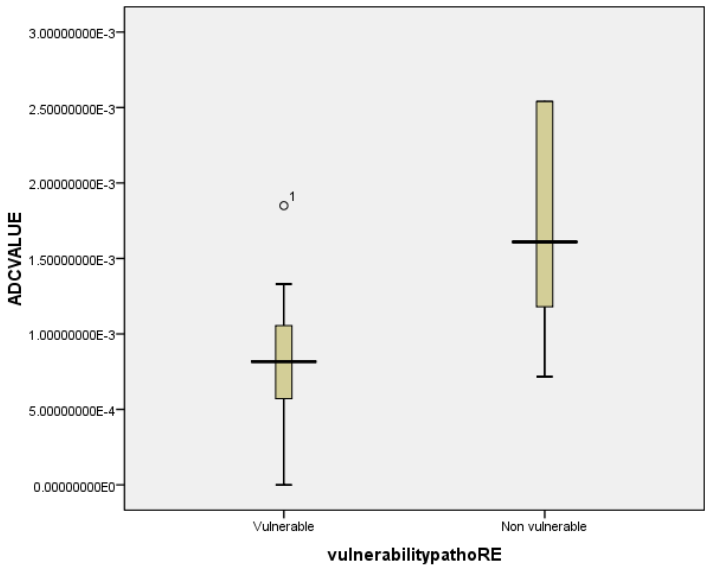

Fig.23: Box plot comparing ADC values between vulnerable and non-vulnerable plaque groups showing significant differences in values.

Lipid Necrotic Core

Table 18: Comparison of ADC mean values between subjects with the presence of lipid necrotic core and absence of the same.				
		No. of study subjects	Mean	Std. Error Mean
ADC VALUE	Lipid necrotic core Present	13	**0.86 x 10^{-3}**	**0.13 x 10^{-3}**
	Lipid necrotic core Absent	10	**1.44 x 10^{-3}**	**0.26 x 10^{-3}**
P value .042 ; 95% CI : 0.022 x10^{-3} - 1.14 x 10^{-3}				

There was a significant difference in mean ADC values between vulnerable groups and non-vulnerable groups. Besides, an independent t-test also revealed the significant difference in mean values in plaques with lipid necrotic core and absent lipid necrotic core.

Intraplaque Hemorrhage

Table 19: Comparison of ADC mean values between subjects with the presence of plaque hemorrhage and absence of the same.

		No. of study subjects	Mean	Std. Error Mean
ADC VALUE	Intra plaque hemorrhage Present	9	**0.751×10^{-3}**	**0.111×10^{-3}**
	Intra plaque hemorrhage `Absent	14	**1.352×10^{-3}**	**0.203×10^{-3}**
P value 0.037; 95% CI : 0.038×10^{-3} - 1.164×10^{-3}				

The mean ADC values between plaques with hemorrhage and without hemorrhage also had a significant difference in values with $p < 0.05$.

ROC ANALYSIS FOR OVERALL PLAQUE VULNERABILITY

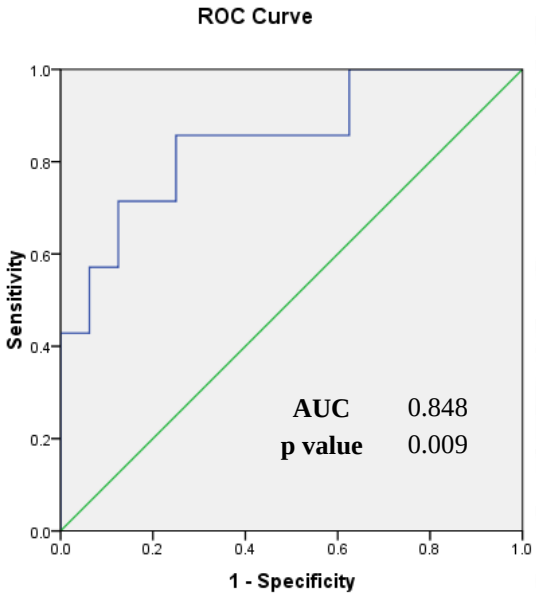

Fig.24: ROC curve analysis of ADC value in the differentiation of non-vulnerable plaque from vulnerable plaque.

For differentiating a non-vulnerable plaque an ADC value of 1.1145 x 10-3 had a sensitivity of 71.4 % and specificity of 81.2 %.

Table 19: Sensitivity and specificity of various ADC values in the detection of plaque vulnerability.

Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
.0000000000	1.000	1.000
.0002055005	1.000	.938
.0004685000	1.000	.875
.0005375000	1.000	.812
.0005710000	1.000	.750
.0006380000	1.000	.688
.0007000000	1.000	.625
.0007490000	.857	.625
.0007895000	.857	.562
.0008160000	.857	.500
.0008440000	.857	.438
.0008655000	.857	.375
.0009485000	.857	.312
.0010450000	.857	.250
.0010800000	.714	.250
.0011450000	**.714**	**.188**
.0012450000	.714	.125
.0013100000	.571	.125
.0014700000	.571	.062
.0017300000	.429	.062
.0021950000	.429	.000
1.0000000000	.000	.000

ILLUSTRATIVE CASES

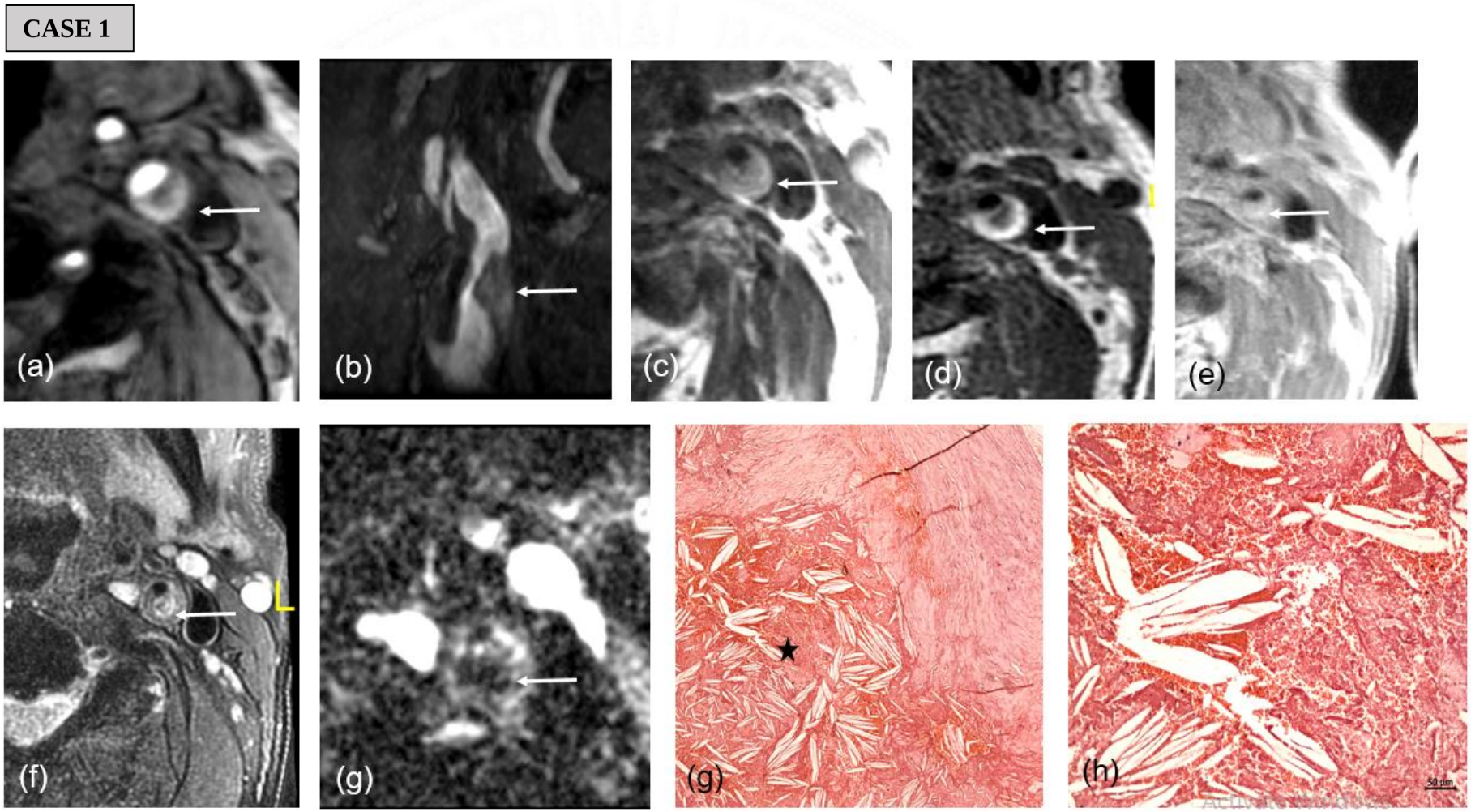

Fig.25: Carotid MR images of an ICA plaque in a 70 year old diabetic male who had symptomatic left MCA stroke, who had NIHS score of 8 at admission, and no prior cerebrovascular events was detected to have 72% stenosis in MR TOF (a,b), with the ICA plaque(arrows) showing TOF(a) and T1(c) hyper intensity indicative of intraplaque hemorrhage. The plaque appeared predominantly hyperintense in T2 (d), PD(e) and T2FS (f). The plaque had average ADC value of 0.83 x 10^{-3} mm^2/sec. Histological images of the same plaque(g- Original magnification 50X, Scale bar 200µm, h- Original magnification 200X, Scale bar 50µm) showing intraplaque haemorrhage (*) containing RBCs admixed with few cholesterol clefts.

CASE 2

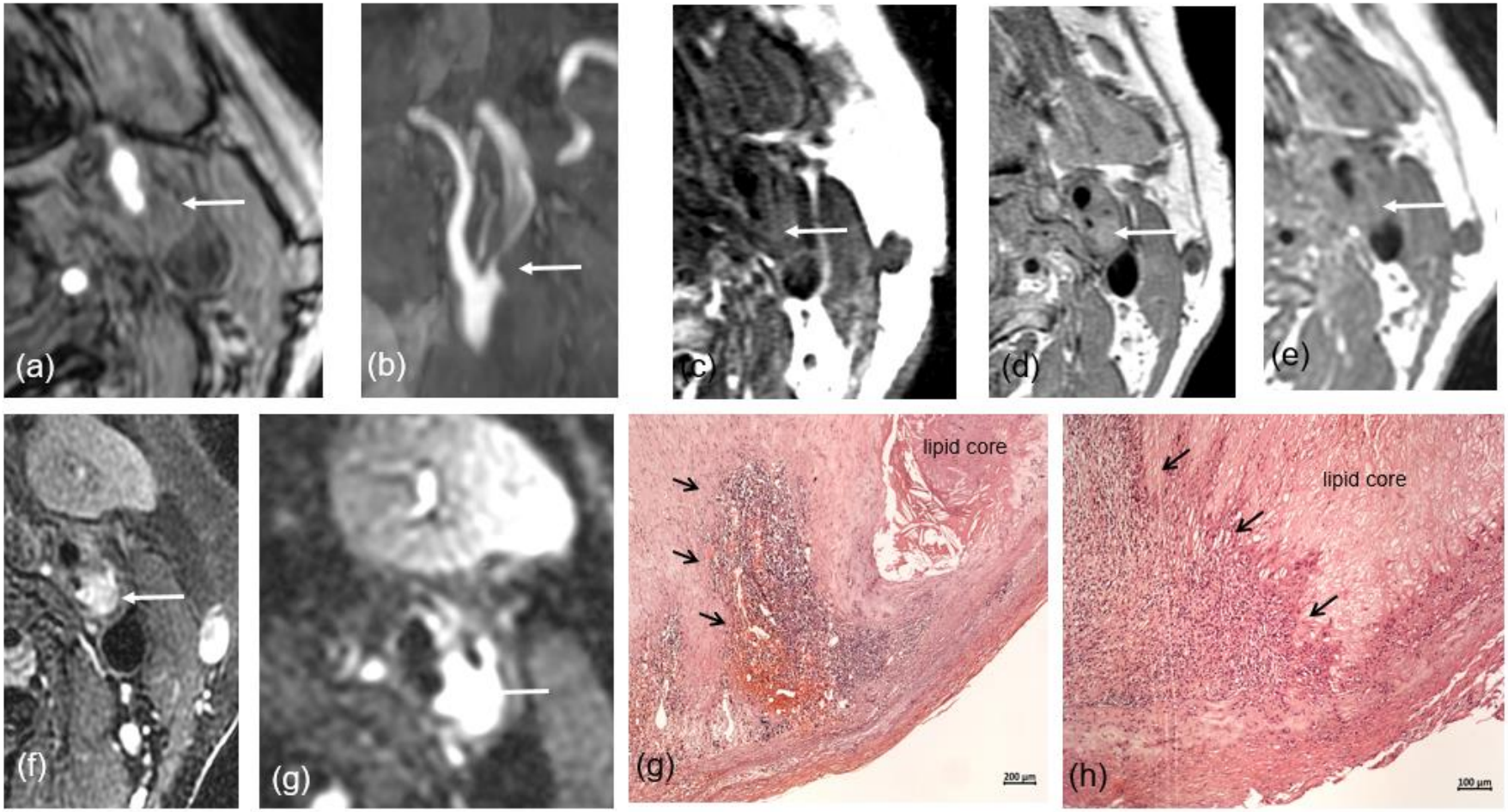

Fig.26: Carotid MR images of 66 year hypertensive female with left ICA stenosis detected following right upper limb paresis. TOF images (*a,b*) showed mildly hyperintense plaque(*arrows*) involving carotid bulb extending into proximal left ICA causing ~ 80% stenosis. T1 image(*c*) showed the plaque to have iso-hyperintense areas which showed hyper intensity in PD(*d*) compared to T2(*e*). The plaque showed hyperintense areas in DWI(*g*) with ADC value of 0.41 x 10^{-3} mm^2/sec. Post endarterectomy, histological analysis showed lipid necrotic core with inflammatory cell infiltrate(*arrows in h - Original magnification 50X, Scale bar 200µm, g - Original magnification 100X, Scale bar 100µm; Haematoxylin and Eosin*).

CASE 3

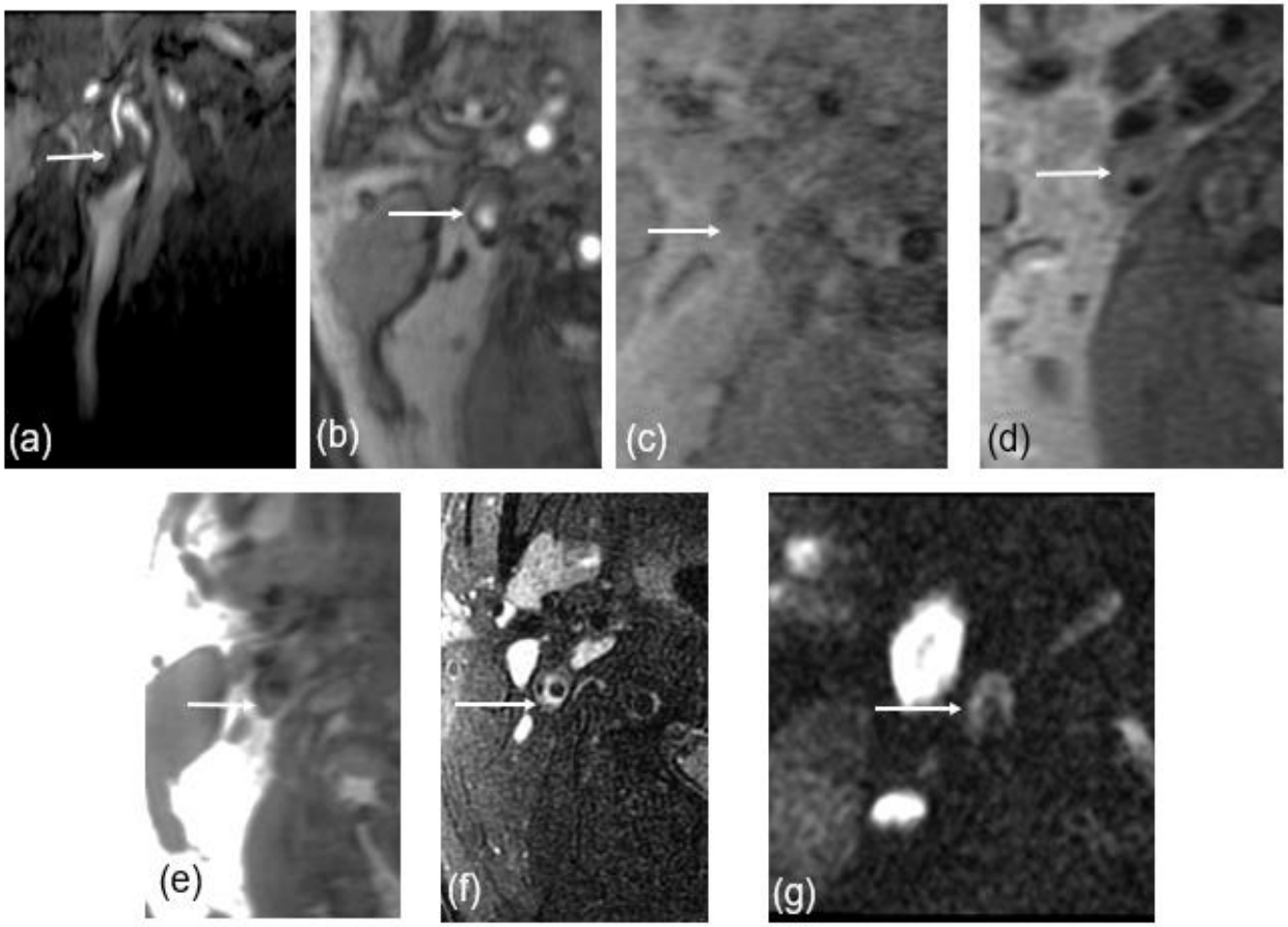

Fig 27:Carotid MR images of a 65 year male with left hemiparesis, who was detected to have right ICA 80% stenosis (*arrows*). His NIHS at admission was 6 with total 2 cerebrovascular events prior to surgery. TOF images(*a,b*) showing right ICA stenosis with axial TOF showing largely preserved periluminal dark band indicative of intact fibrous cap. T1 image (*c*) showed mildly increased signal with T2 (*d*)and PD(*e*) showing the plaque to have largely similar intensities. T2 FS (*f*) also showed the luminal stenosis with DWI image(*g*) with ADC value of 1.290 x 10^{-3} mm^2/sec.

CASE 4

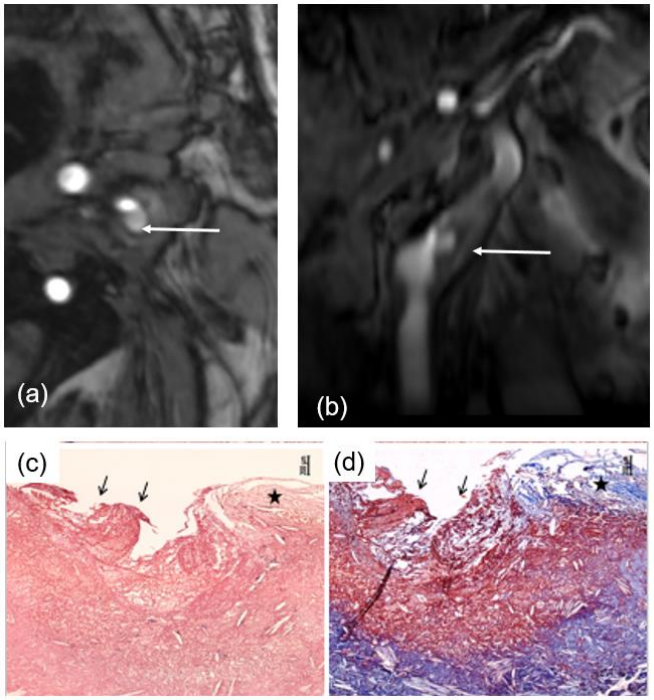

Fig.28: MR TOF axial(*a*) and oblique sagittal(*b*) in a 67 year old male with diabetes, hypertension and dyslipidemia. TOF images showed the irregularity in the luminal surface with deep ulceration(*arrows*) indicative of fibrous cap rupture. Histological images (*c: Haematoxylin and Eosin, d: Masson Trichrome, Original magnification 50X, Scale bar 200µm*) showing the plaque with probable cap rupture with thrombus adherent to lipid core (*arrows*) and remnants of cap (*)

CASE 5

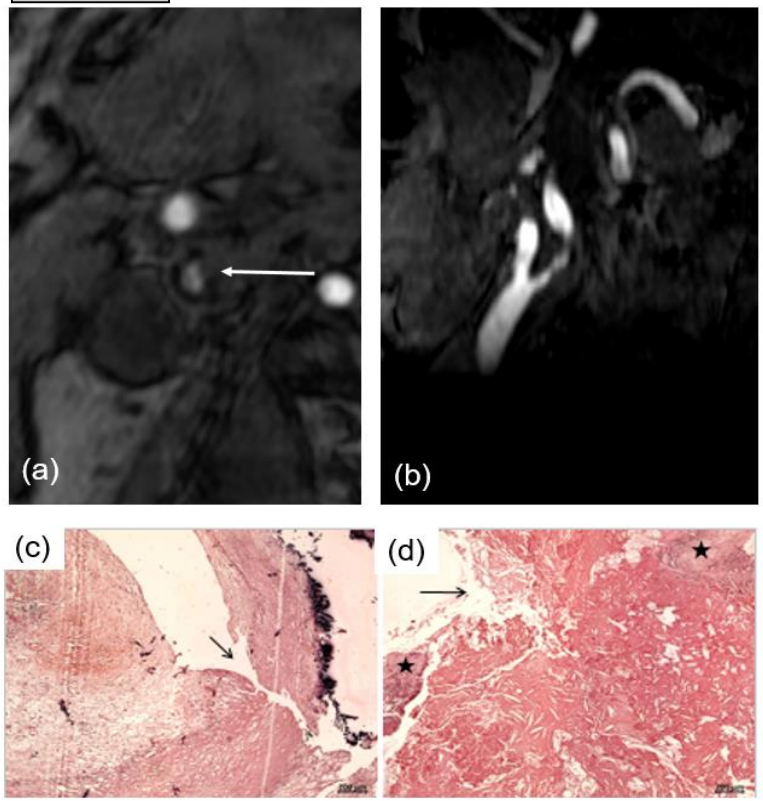

Fig.29 : MR TOF axial(*a*) and oblique sagittal(*b*) in a 64 year old male with total of 7 cerebrovascular events and no comorbidities, depicting the deficient(*arrow*) dark band in axial TOF image. Histological images (c,d : *Haematoxylin and Eosin*) depicting the cap rupture (*arrows*) with remnants of cap (*)

DISCUSSION

DISCUSSION

The crude stroke prevalence in different parts of India ranged from 44.29 to 559/100,000 persons during the past two decades. The cumulative incidence of stroke in India ranged from 105 to 152/100,000 persons per year during the past two decades in different parts of the country(7).

This study aimed at demonstrating a correlation of in vivo 3T MR plaque and lumen findings with histopathology with the use of non-contrast sequences. The ability to noninvasively characterize carotid plaque on 3T MR imaging extends our knowledge of which distinctive wall features are associated with symptoms to include a patient population that does not meet established criteria for surgical resection. A total of 27 patients underwent, carotid plaque MRI and subsequent endarterectomy as part of the study. 23 cases were available finally for analysis as 4 patients were excluded due to technical issues in imaging and/or pathological evaluation.

Only limited such studies using only non-contrast sequences with DWI were available on literature search internationally, with non from India published so far. Most of the studies available have analyzed the same in 1.5T MRI with recently few papers in 3T with studies limited to specific plaque components only(31,54,64,65). Also, there are only limited studies that have analyzed non-contrast sequences alone for evaluation using a 3T MRI carotid coil(66,67).

DEMOGRAPHICS

The majority (65.2 %) of the study subjects were in the age group of 60-70 years. This was similar to the data of incidence of stroke in the Trivandrum Stroke Registry in which the median age was ~ 67 years(68). The median age of our study population was 66 years. This was also the case with most registry data on stroke(69).

In our study on candidates who underwent endarterectomy eventually, the youngest patient was 50 years, with him being the only young stroke patient in the study. Male to female

ratio of the subjects was 1.87 in our study, which indicated that relatively more males underwent endarterectomy secondary to symptomatic carotid artery stenosis. This has to be emphasized as data from the Trivandrum stroke registry, revealed a higher incidence of stroke-related events in females in the urban population with only a slight increase in males in the rural population.

RISK FACTORS

The study had only 1 asymptomatic patient with the rest of the 22 subjects having carotid stenosis related symptoms. Hypertension (86.9%) was the most common risk factor present in the study population followed by diabetes (65.2%), dyslipidemia (47%), and smoking (34.7%). This was similar to the risk factor in population with stroke incidence. However, among risk factors, the incidence of coronary artery disease, peripheral vascular disease, and renal disease in previously described literature for stroke, is higher(70–73). However, in our study, there were no cases of CAD/ Renal disease and only 2 cases with peripheral vascular disease. This may be attributed to the fact that patients who had coronary artery disease / renal disease had a higher risk for surgical morbidity/ mortality and hence were not included as surgical candidates, instead underwent carotid stenting.

ASSOCIATION OF COMORBIDITIES WITH PATHOLOGICAL PLAQUE VULNERABILITY CHARACTERISTICS

Hypertension, dyslipidemia, and male gender were associated with the detection of unstable plaques in a study by Rovella et al, which evaluated 390 cases(74). However, the various risk factors were analyzed with plaque vulnerability with none of the parameters found to be statistically significant in our study. The sample size is too small for assessment of risk factor and outcome measures, hence detailed evaluation with a larger sample size may be more reliable. So was also the case with the mean number of prior cerebrovascular events and serum cholesterol levels being found to be higher in the vulnerable plaque group.

CAROTID STENOSIS WITH CT AND MRI

In our analysis, CTA and MRA stenosis measurements showed a good correlation (Pearson correlation coefficient 0.748) confirming most of the studies available in the literature. Meta-analysis has shown that the overall sensitivity and specificity of TOF MRA to diagnose severe stenosis are 91.2% and 82.3% respectively(75). Also in the study by Lell et al, in which CTA and MRA TOF was showed high concordance(difference 0.6%; CI: -3,4.3%)(76). CTA and MRA are found to be equally sensitive but differ in specificity with the specificity of CTA being always higher(77). MRA suffers from the flow signal loss, mainly in case of turbulent flow and slow flow, leading to an inaccurate measurement of stenosis degree. In such a scenario, contrast-enhanced MRA has an advantage. 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). Meta-analysis studies of all three imaging modalities show that MRA is the most sensitive diagnostic tool for carotid stenosis, followed by DUS, with CTA being the least sensitive. In terms of specificity, both MRA and CTA are reasonably good (in the range of 90% to 95%), followed by DUS (79). Radiation exposure in CTA is an issue compared to Doppler sonography or MRA, especially in patients in the mild to moderate stenosis group, who will require repeated imaging follow up.

PLAQUE CHARACTERISTICS IN 3T MR IMAGING

INTRAPLAQUE HEMORRHAGE

Intraplaque hemorrhage is thought to develop due to the neoangiogenesis within the plaque, with leaky vessels(80). Our results indicate that intraplaque assessment with our non-contrast protocol had the strongest agreement with histology (k 0.817) with a sensitivity and specificity of 88.9% and 92.9% respectively. This was corresponding to the recent meta-analysis by Zhou et al, in which overall sensitivity and specificity of MR in hemorrhage detection were 87% and 92% respectively(81). The presence of IPH was associated with a

hazard ratio of 5.69 for cerebrovascular events and an overall annualized event rate of 17.71% (82). Most studies in the meta-analysis were done on a 1.5 T MRI with largely non-contrast sequences as in our study. Albuquerque et al additionally evaluated specifically the ability to detect recent hemorrhage using T1 weighted magnetisation prepared 3D gradient-echo sequence with a sensitivity and specificity of more than 95% (83). MP-RAGE and SNAP are newer sequences that have also been evaluated in the detection of hemorrhage especially in the carotids with promising results(51,84). Though we did use a spoiled gradient 3D sequence in CUBE T1 for evaluation, which offers the advantage for detection of hemorrhage as well, the same was not evaluated as part of the present study and is planned for analysis separately in future. Detecting the absence of hemorrhage in a carotid plaque is also clinically relevant as it indicates a benign course of the disease even in symptomatic patients with >50% stenosis (85). The low ADC values in IPH are described in previous studies and hypothesised to be due to inflammatory nature of the plaque and coexistent LRNC(48).

LIPID NECROTIC CORE

MR detection of lipid necrotic core had a moderate agreement with histological findings (k 0.493; Sensitivity 61.5%; Specificity 90 %). Prior studies relied mostly on T1W sequences along with post-contrast to identify LRNC, however, the present study didn't have a post-contrast assessment. Saam et al. used comparable sequences when considering LRNC areas wherein the sensitivity and specificity was 92% and 65% respectively with k 0.73.>2 mm^2, and with a good correlation between MRI and histology (R ¼ 0.75, P < 0.001)(34). However, significant inter-observer variability was described in the study by Touze et al in the detection of the lipid component(86), which may be the reason for moderate agreement in our study compared to the stronger association with hemorrhage detection. Also, contrast administration increased the detection of the necrotic core in the above studies. However, this issue may be overcome with the addition of diffusion-weighted imaging with ADC value assessment, which revealed a significant difference in the identification of the lipid necrotic

plaque. Young et al. also demonstrated by performing a DWI sequence that LRNC could be differentiated from other plaque components in vivo(45).

FIBROUS CAP STATUS

The least agreement was in the detection of the status of a fibrous cap in our non-contrast MR evaluation which was only fair (k 0.258; Sensitivity 33%, Specificity 100%). However, the high specificity confirms the cap rupture if seen in the MR evaluation. 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. Most studies have relied on post-contrast sequences as well for its better depiction(33,87), which we have not evaluated as part of this study. The method used for analysis in this study was the one described by Hatsukami, Thirty-six sites were available for comparison between MRI and histology. There was a high level of agreement between MRI and histological findings: 89% agreement, κ (95% CI)=0.83 (0.67 to 1.0), weighted κ=0.87. Spearman's correlation coefficient was 0.88 (significant to the 0.01 level). The above study was done on a 1.5 T MR scanner. More evaluation for validation using 3T MR protocols and further optimization needs to be done for better validation of fibrous cap assessment using the non-contrast sequences.

The utility of MR evaluation of carotids may also be done as a marker for risk stratification for cardiovascular events as well. Few studies including by Wasserman et al. demonstrated that in asymptomatic individuals with thickened carotid walls, the presence of lipid core by MRI is associated with total plasma cholesterol, as well as increased risk of cardiac events(16,88)**.**

DIFFUSION AND ADC IN CAROTID PLAQUE ASSESSMENT

DWI was found to be applicable for the assessment of carotid plaque by Kim et al(46). Kim did both in vivo and ex vivo mean ADC measurement on 8 study subjects and compared results and documented detection of the lipid necrotic core. In his study, the mean ADC for

normal vessel wall, lipid-rich necrotic core, and hemorrhage were 1.27 X 10^{-3}, 0.38 x $10^{-3,}$ and 0.98 x 10^{-3} mm^2/s respectively. 2D ss-IMIV-DWEPI was used in this study to avoid the geometrical distortion in EPI done in a Siemens 3T MRI using custom-designed dual-element phased-array surface coils. Subsequently, 3D DWI was also stated for a better depiction of the vessel wall by Xie et al, however, no histological correlation was done as part of the study(89). In our assessment, a significant difference in mean ADC values between overall vulnerable and non-vulnerable plaques was depicted with a cut off of 1.24 x 10^{-3} mm^2/sec, with a sensitivity of 75% and specificity of 79%. This was despite the overall moderate image quality compared to a few of the recent studies which used 3D DWI, at the cost of increased acquisition time. Our mean ADC value for lipid necrotic core was 0.86 x 10^{-3} mm^2/s which was relatively similar to values obtained by Ota et al(48). Most of the studies (including Ota et al) mentioned have used b-values of 500 for assessment, as in our study. All our study subjects had moderate to severe stenosis (> 50%), thus visualization of the plaque in our protocols was not much of an issue. Hence, its applicability in patients with 50-70% stenosis may be potentially used for management decision making. However, the utility in subjects with <50% stenosis with reduced plaque burden may be limited. The same was also the case with the study by Young et al, with ADC value for lipid core being 0.73 x 10^{-3} mm^2/sec using EPI- DWI sequence (45).In our study ADC values were also able to significantly able to differentiate between intraplaque hemorrhage, however, values showed overlap with that of lipid necrotic core, probably due to the presence of coexistence of hemorrhage and necrosis in few of the study samples combined with the inherent errors of the sequence used for assessment. Further evaluation with a larger sample size maybe needed for the same.

LIMITATIONS

Inter and intra observer variability was an entity not assessed in this study, which would have assessed the reproducibility of this modality. Also, a larger part of the evaluation in this study was qualitative with quantitative parameter limited to diffusion values as the study was

part of an initial stage validation study in our Institute. Unavailability of the newer motion correction sequences may also have influenced image acquisition. The quantitative analysis of the size/percentage volume lipid-rich necrotic core/hemorrhage was not assessed. As part of further continuing study, assessment with dedicated carotid plaque software and MR newer sequences are being planned especially in subjects with less than 70 % carotid stenosis.

Prospective analysis of the carotid stenosis patients who are medically managed is also being planned as the next stage evaluation since the strength of MRI to predict the risk of future events also needs to be addressed.

The inclusion of only >50% stenosis subjects who mostly had prior cerebrovascular events is in itself a selection bias as is the case in all similar studies in the literature. Evaluation with much larger samples may be vital in validating the findings and its utility.

CONCLUSION

CONCLUSION

This in vivo 3T MR imaging of patients demonstrates several plaque components that are correlated with recent carotid thromboembolic symptoms of the affected side. These preliminary results indicate the MR utility of the assessment of stenosis along with plaque characteristics. The carotid MR imaging may distinguish stable from unstable lesions, particularly in individuals with mild/moderate carotid stenosis in whom the role of surgical intervention is currently unclear.

- This easy to apply less than 30 min non-contrast protocol can be used for evaluation of carotid plaque vulnerability on a 3T MRI with an overall moderate agreement with histological plaque characteristics. Hence, enabling its use even in patients with renal dysfunction and in follow up of patients on medical management.
- The strongest correlation in plaque vulnerability on a 3T MRI scanner with the study protocol used was noted to be with the detection of intraplaque hemorrhage in the present study.
- The potential benefit of DWI of the carotid artery in delineating plaque characteristics was also validated. The use of DWI and ADC value assessment may prove to be a quantitative parameter for the detection of plaque vulnerability with the ability to differentiate various plaque components.
- A good correlation was noted between CT angiography and non-contrast MR angiography assessment of carotid stenosis.

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ANNEXURES

INFORMATION SHEET

TITLE OF THE STUDY: ASSESSMENT OF CAROTID PLAQUE VULNERABILITY USING 3T MAGNETIC RESONANCE IMAGING AND ITS CORRELATION WITH CAROTID ENDARTERECTOMY SPECIMEN HISTOPATHOLOGY

Study number:
Participant's name: Date of Birth / Age (in years): son/daughter of
_____

You have been informed that there is a marked narrowing in one of the major vessels supplying your brain parenchyma (namely Internal Carotid Artery), which is believed to be the cause of your neurological symptoms. As part of treatment, a procedure called Carotid Endarterectomy is planned for the same to prevent future cerebrovascular events. A carotid endarterectomy is a surgical procedure in which a doctor removes fatty deposits from one of two (Right or left) main arteries in the neck. These blood vessels which are called carotid arteries supply blood to the brain. The disease process that causes the buildup of fat and other material on the artery walls is called atherosclerosis. The fatty deposit is called plaque while the narrowing of the artery is known as stenosis. The degree of stenosis is usually expressed as a percentage of the normal diameter of the opening. As a part of the clinical evaluation of your disease to plan the treatment or for follow up your disease you will have undergone or will be undergoing MR imaging.

You are being requested to participate in a study to evaluate the role of 3T MRI in the assessment of carotid plaques and to analyze the possibility of predicting the plaque vulnerability. Participating in this study, in which only data from the investigations you have undergone for your treatment will be used, will in no way influence treatment decisions.

What is 3T MRI and does it have any harmful effects?

3T MRI is an advanced imaging technique which uses radio waves and a powerful magnet linked to a computer are used to make detailed pictures of areas inside the body. These pictures can show the difference between normal and abnormal tissue. 3T MRI has a stronger magnet and makes better images of organs and soft tissue than other types of MRI do. It is used to make images of the brain, the spine, the soft tissue of joints, and the inside of bones and blood vessels. There is no risk of radiation exposure. This test is vital in the diagnosis of your condition, its treatment, and for follow up subsequently.

If you take part what will you have to do?

For this study, we'll be using some of the data like history and other clinical details, Imaging details (MRI & CTA), treatment details, and pathological details of the specimen sent for analysis following the surgery. No additional cost will be incurred /no additional drugs will be used and there are no additional risks as a part of the research.

Analysis of these data may or may not be useful for you later, but this is likely to give more understanding of this disease and treatment, for the benefit of future generations. You understand that strict confidentiality will be maintained.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study-related injury?

This study only analyzes the results of your investigation and treatment details and thus we do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at this institute by the experienced team of medical professionals. We are unable to provide any monetary compensation, however.

Will you have to pay for the study?

The study will only analyze the results of the investigations and treatment which you will undergo in the natural process of your treatment at this institute and no extra cost will be borne by you for this particular study.

What happens after the study is over?

You may or may not benefit from this study, after the study we will be able to assess the utility of 3T MR carotid plaque imaging in predicting the risk of embolization in the future; it may thus benefit other patients with similar illness.

Will your details be kept confidential?

The results of this study may be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr. Ajay Alex (Tel: 9895553639) or email:
drajayalex@sctimst.ac.in/ contact IEC member secretary (Tel: 0471-2524263)

കാര്യവിവരണപത്രം

കരോട്ടിഡ് പ്ലേക് അപായാവസ്ഥയുടെ വിലയിരുത്തലിൽ, 3റ്റി മാഗനറ്റിക് റെസൊണൻസ് ചിത്രീകരണവും കരോട്ടിഡ് എൻഡറാക്ടെറെക്ടമി മാതൃകയുടെ ഹിസ്റ്റോപതോളജിയുമായുള്ള പാരസ്പര്യം.

പഠനനമ്പർ

പങ്കെടുക്കുന്നയാളുടെ പേര്.....................................

ജനനതീയതി/വയസ്സ്(വർഷത്തിൽ)..........

മകൻ/മകൾ ....

താങ്കളുടെ തലച്ചോറിലേക്ക് രക്തം നൽകുന്ന മഹാധമനികളിലൊന്ന് (ഉള്ളിലുള്ള കരോട്ടിഡ് ആർട്ടറി എന്ന് വിളിക്കുന്ന) പ്രകടമായവിധം ഇടുങ്ങിയിട്ടുണ്ടെന്നും ആയതാണ് താങ്കളുടെ ന്യൂറോളജിക്കൽ ലക്ഷണങ്ങൾക്ക് കാരണമെന്നും വിശ്വസിക്കുന്നതായി താങ്കളെ അറിയിച്ചിട്ടുണ്ട്. ഭാവിയിൽ കാർഡിയോ വാസ്ക്കുലർ സംഭവങ്ങൾ ഉണ്ടായേക്കാവുന്നത് തടയാൻ, ,ചികിത്സയുടെ ഭാഗമായി, കരോട്ടിഡ് എൻഡറടെറെക്ടമി എന്നു വിളിക്കപ്പെടുന്ന നടപടി ആസൂത്രണം ചെയ്യുകയാണ്.

കഴുത്തിലെ രണ്ട് (ഇടതുവശത്തെയോ വലതുവശത്തെയോ) മഹാധമനികളൊന്നിലുള്ള കൊഴുപ്പ് നിക്ഷേപം നീക്കംചെയ്യാൻ ഡോക്ടർ നടത്തുന്ന നടപടിയായ കരോട്ടിഡ് എൻഡറാക്ടെറെക്ടമി എന്നത് ഒരു ശസ്ത്രക്രിയയാണ്. കരോട്ടിഡ് മഹാധമനികളെന്ന് വിളിക്കപ്പെടുന്ന ഈ രക്തക്കുഴലുകളാണ് തലച്ചോറിലേക്ക് രക്തം നൽകുന്നത്. ധമനിയുടെ ഭിത്തിയിൽ കൊഴുപ്പും മറ്റ് പദാർത്ഥങ്ങളും നിക്ഷേപിക്കപ്പെടുന്ന രോഗ പ്രക്രിയയെയാണ് അതിറോസ്ക്ലിറോസിസ് എന്ന് വിളിക്കപ്പെടുന്നത്. കൊഴുപ്പിന്റെ നിക്ഷേപത്തെ പ്ലേക് എന്നും ധമനിയുടെ ഭിത്തികളുടെ ഇടുങ്ങലിനെ സ്റ്റെനോസിസ് എന്നും പറയുന്നു. സാധാരണയുള്ള രക്തക്കുഴലിന്റെ വ്യാസത്തിന്റെ ശതമാനമായാണ് സ്റ്റെനോസിസ്സിന്റെ അളവ് പ്രകടിപ്പിക്കുന്നത്. താങ്കളുടെ രോഗത്തിന്റെ വൈദ്യാലയ അപഗ്രഥനത്തിന്റെ ഭാഗമായുള്ള ആസൂത്രണത്തിനോ തുടർചികിത്സക്കോ താങ്കൾ എം.ആർ ചിത്രീകരണത്തിന് വിധേയമാകേണ്ടതുണ്ട്.

കരോട്ടിഡ് പ്ലേക്കിന്റെ വിലയിരുത്തലിൽ 3റ്റി എം.ആർ.ഐയുടെ പങ്ക് അപഗ്രഥിക്കാനും പ്ലേക് അപായാവസ്ഥ പ്രവചിക്കാനാകുമോയെന്ന് വിലയിരുത്താനുമായി നടത്തുന്ന ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ താങ്കളോട് അഭ്യർത്ഥിക്കുന്നു. താങ്കൾ വിധേയമായ പരിശോധനകളുടെ വിവരങ്ങൾ ഉപയോഗിക്കുക മാത്രം ചെയ്യുന്ന ഈ പഠനം താങ്കളുടെ ചികിത്സാതീരുമാനങ്ങളെ ഒരു വിധ ത്തിലും സ്വാധീനിക്കില്ല.

എന്താണ് 3റ്റി അതിനെന്തെങ്കിലും ദോഷവശങ്ങളുണ്ടോ

റേഡിയോ തരംഗങ്ങളും ഒരു ശക്തമായ കാന്തവും കമ്പ്യൂട്ടറിനോട് ബന്ധിപ്പിച്ച് ശരീരത്തിനുള്ളിലെ ഭാഗങ്ങളുടെ വിശദമായ ചിത്രങ്ങളെടുക്കുന്ന ആധുനീകമായ ചിത്രീകരണ സങ്കേതമാണ് 3റ്റി എംആർഐ. ഈ ചിത്രങ്ങൾക്ക് സാധാരണവും അസാധാരണവുമായ കലകളുടെ വ്യത്യാസങ്ങൾ കാണിക്കാനാകും. മറ്റ് എംആർഐയെക്കാൾ നന്നായി ശരീരഭാഗങ്ങളുടെയും മൃദുവായ കലകളു ടെയും ചിത്രങ്ങൾ സൃഷ്ടിക്കാൻ കൂടുതൽ ശക്തമായ ഒരു കാന്തമുള്ള 3റ്റി എംആർഐ ക്ക് കഴി യും. തലച്ചോർ, നട്ടെല്ല്, മുട്ടുകളുടെ മൃദു കലകൾ, എല്ലിന്റെയും രക്തക്കുഴലുകളുടെയും

ഉൾഭാഗം എന്നിവയുടെ ചിത്രങ്ങളുണ്ടാക്കാൻ ഇതുപയോഗിക്കുന്നു. റേഡിയേഷൻ അപായം ഇല്ല. താങ്കളുടെ അവസ്ഥക്കും, ചികിത്സക്കും അനുബന്ധമായ തുടർ ചികിത്സക്കും ഇത് അത്യന്താപേക്ഷിതമാണ്.

പങ്കെടുക്കുകയാണെങ്കിൽ താങ്കളെന്തു ചെയ്യണം**?**

ഈ പഠനത്തിനായി ഞങ്ങൾ താങ്കളുടെ ചരിത്രം, മറ്റ് പരിശോധനാ വിശദാംശങ്ങൾ, ചിത്രീകരണ വിശദാംശങ്ങൾ (എംആർഐയും സിറ്റിയും), ചികിത്സാ വിശദാംശങ്ങൾ, ശസ്ത്രക്രിയക്കുശേഷം അയച്ച മാതൃകകളുടെ പതോളജിപരമായ വിശദാംശങ്ങൾ എന്നിവ ഉപയോഗിക്കും.

അധികമായ ചിലവ് ഉണ്ടാകില്ല/അധികം മരുന്നുകൾ ഉപയോഗിക്കില്ല, ഗവേഷണത്തിന്റെ ഭാഗമായി അധികം അപായവുമുണ്ടാകില്ല. വിവരങ്ങളുടെ അപഗ്രഥനം താങ്കൾക്ക് ഉപയോഗപ്രദമായേക്കില്ല, പക്ഷേ അത് ഈ രോഗത്തെപ്പറ്റി കൂടുതൽ മനസ്സിലാക്കാനും അതുവഴി ഭാവിതലമുറക്ക് പ്രയോജനപ്രദമാകാനും ഇടയുണ്ട്. കർശനമായ രഹസ്യസ്വഭാവം നിലനിർത്തുമെന്ന് താങ്കൾ മനസ്സിലാക്കണം.

പഠനമാരംഭിച്ചശേഷം താങ്കൾക്ക് പിൻമാറാമോ**?**

താങ്കളുടെ പഠനത്തിലുള്ള പങ്കാളിത്തം തികച്ചും സ്വമേധയായാണ്, പഠനത്തിലെ പങ്കാളിത്തത്തിൽ നിന്നും പിൻമാറാൻ തീരുമാനമെടുക്കാൻ താങ്കൾക്ക് സ്വാതന്ത്ര്യമുണ്ട്. താങ്കളങ്ങിനെ ചെയ്താലും താങ്കളുടെ ഈ ആശുപത്രിയിലെ പതിവ് ചികിത്സയെ ഒരുവിധത്തിലും ബാധിക്കില്ല.

പഠനവുമായി ബന്ധപ്പെട്ട് താങ്കൾക്ക് എന്തെങ്കിലും പരുക്കുണ്ടായാലെന്ത് സംഭവിക്കും **?**

താങ്കളുടെ പരിശോധനകളുടെയും ചികിത്സയുടെയും ഫലങ്ങൾ അപഗ്രഥിക്കുകമാത്രമാണ് ഈ പഠനം ചെയ്യുന്നത് എന്നതിനാൽ താങ്കൾക്ക് പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് പരുക്കുകളുണ്ടാകുമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നില്ല. പക്ഷേ പഠനവുമായി ബന്ധപ്പെട്ട് താങ്കൾക്കെന്തെങ്കിലും പാർശ്വഫലളങ്ങളോ പ്രശ്നങ്ങളോ ഉണ്ടായാൽ താങ്കൾക്ക് അധികച്ചിലവുണ്ടാകാതെ ഈ ആശുപത്രിയിൽ ചികിത്സിക്കും. എന്നിരുന്നാലും സാമ്പത്തികമായ നഷ്ടപരിഹാരം നൽകാനാവില്ല.

പഠനത്തിനായി താങ്കൾ പണം ചിലവാക്കണോ?

ഈ ആശുപത്രിയിൽ താങ്കൾ സ്വാഭാവികമായി ചികിത്സക്കുവേണ്ടി ചെയ്യുന്ന പരിശോധനകളുടെയും ചികിത്സയുടെയും ഫലങ്ങൾ അപഗ്രഥിക്കുകമാത്രമാണ് ഈ പഠനം ചെയ്യുന്നത്. ഈ പഠനത്തിനായി താങ്കൾ അധികച്ചിലവൊന്നും വഹിക്കേണ്ടതില്ല.

പഠനം കഴിഞ്ഞശേഷം എന്തു സംഭവിക്കും**?**

താങ്കൾക്ക് ഈ പഠനംകൊണ്ട് നേട്ടം ഉണ്ടാവുകയോ ഇല്ലാതിരിക്കുകയോ ചെയ്യാം. പഠനത്തിനവസാനം 3റ്റി എംആർഐയുടെ കാരോട്ടിഡ് പ്ലേക്കിന്റെ ചിത്രീകരണത്തിലും ഭാവിയിൽ തടസ്സമുണ്ടാകാനുള്ള സാദ്ധ്യത പ്രവചിക്കുന്നതിലുമുള്ള പ്രയോജനക്ഷമത വിലയിരുത്തും. സമാനമായ രോഗമുള്ള മറ്റു രോഗികൾക്ക് അങ്ങിനെ നേട്ടമുണ്ടായേക്കാം.

താങ്കളുടെ വ്യക്തിവിവരങ്ങൾ രഹസ്യമായിരിക്കുമോ?

പഠനഫലങ്ങൾ ഒരു വൈദ്യശാസ്ത്ര ജേർണലിൽ പ്രസിദ്ധീകരണത്തിന് നൽകുമെങ്കിലും താങ്കളെ വ്യക്തിപരമായി തിരിച്ചറിയാനിടയാക്കുന്നതൊന്നും പ്രസിദ്ധീകരണത്തിലോ, പഠനഫലങ്ങളുടെ

പ്രദർശനത്തിലോ ഉണ്ടാവില്ല. എന്നിരുന്നാലും താങ്കൾ പങ്കെടുക്കുകയാണെങ്കിൽ താങ്കളുടെ ചികിത്സാ വിവരങ്ങൾ പഠനവുമായി ബന്ധപ്പെട്ടവർ താങ്കളുടെ അധികമായ സമ്മതമില്ലാതെ പരിശോധിച്ചേക്കാം.

താങ്കൾക്ക് കൂടുതൽ എന്തെങ്കിലും ചോദ്യങ്ങൾ ഉണ്ടെങ്കിൽ ദയവായി ഡോ. അജയ് അലക്സിനോട് ചോദിക്കുക, (ഫോൺ: 9895553639). ഇമെയിൽ. drajayalex@sctimst.ac.in

ദയവായി സ്ഥാപനത്തിലെ നൈതീക കമ്മിറ്റി മെംമ്പർ സെക്രട്ടറി ഡോ. മാല രാമനാഥനെ ബന്ധപ്പെടാം. ഫോൺ 04712524234, email: iec.mem.sec@sctimst.ac.in

CONSENT FORM

TITLE OF THE STUDY: ASSESSMENT OF CAROTID PLAQUE VULNERABILITY USING 3T MAGNETIC RESONANCE IMAGING AND ITS CORRELATION WITH CAROTID ENDARTERECTOMY SPECIMEN HISTOPATHOLOGY

Study number:

Participant's name: Date of Birth / Age (in years):

I_____

_____, Son/daughter of _____ (Please

tick boxes)

• Declare that I have read the above information provided to me regarding the study: 'Assessment Of Carotid Plaque Vulnerability Using 3T Magnetic Resonance Imaging and its Correlation with Carotid Endarterectomy Specimen Histopathology' and have clarified any doubts that I had. [ ]

• I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights. [ ]

• I also understand that study investigator will be using some of the data like history and other clinical details, Imaging details (MRI & CTA), treatment details, and pathological details which I undergo in hospital. [ ]

• I also understand that no additional cost will be incurred /no additional drugs will be used and there are no additional risks as a part of the research. [ ]

• I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access.[ ]

• I understand that my identity will not be revealed in any information released to third parties or published. [ ]

• I voluntarily agree to take part in this study. [ ]

• I received a copy of this signed consent form. [ ]

Name: Signature: Date: Name of witness:

Relation to participant:

(Person Obtaining Consent) I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

_____

_____ Name and Signature of Person

Obtaining Consent Principal Investigator.

സമ്മതപത്രം

കരോട്ടിഡ് പ്ലേക് അപായാവസ്ഥയുടെ വിലയിരുത്തലിൽ, 3റ്റി മാഗനറ്റിക് റെസൊണൻസ് ചിത്രീകരണവും കരോട്ടിഡ് എൻഡറടെറെക്ടമി മാതൃകയുടെ ഹിസ്റ്റോപതോളജിയുമായുള്ള പാരസ്പര്യം

ഞാൻ (പങ്കെടുക്കുന്നയാളുടെ പേര് ..... ജനനതീയതി/വയസ്സ് (വർഷത്തിൽ) ..... മകൻ/മകൾ..... (ദയവായി പ്രസക്തമായ കോളങ്ങൾ അടയാളപ്പെടുത്തുക)

- മുകളിൽപറഞ്ഞ കരോട്ടിഡ് പ്ലേക് അപായാവസ്ഥയുടെ വിലയിരുത്തലിൽ, 3റ്റി മാഗനറ്റിക് റെസൊണൻസ് ചിത്രീകരണവും കരോട്ടിഡ് എൻഡറടെറെക്ടമി മാതൃകയുടെ ഹിസ്റ്റോപതോളജിയുമായുള്ള പാരസ്പര്യം എന്ന പഠനസംബന്ധമായി എനിക്ക് നൽകിയ വിവരങ്ങൾ വായിച്ചതായും എനിക്കുണ്ടായ സംശയങ്ങൾ പരിഹരിച്ചതായും ഞാൻ പ്രസ്താവിക്കുന്നു.[ ]

- എന്റെ ഈ പഠനത്തിലുള്ള പങ്കാളിത്തം സ്വമേധയായുള്ളതാണെന്നും, എനിക്ക് ഒരു കാരണവും കൂടാതെ ഏതുസമയത്തും, എനിക്കുള്ള വൈദ്യശുശ്രൂഷയെയോ നിയമപരമായ അവകാശങ്ങളെയോ ബാധിക്കാതെ പിൻവാങ്ങാമെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- എന്റെ ചരിത്രം, ഈ ആശുപത്രിയിലെ പരിശോധനാ വിശദാംശങ്ങൾ, ചിത്രീകരണ വിശദാംശങ്ങൾ (എംആർഐയും സിറ്റിയും), ചികിത്സാ വിശദാംശങ്ങൾ, ശസ്ത്രക്രിയക്കുശേഷം അയച്ച ഭാഗങ്ങളുടെ പതോളജിപരമായ വിശദാംശങ്ങൾ എന്നിവ പഠന ഗവേഷകർ ഉപയോഗിക്കുമെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- ഗവേഷണത്തിന്റെ ഭാഗമായി അധികച്ചിലവോ അധികം മരുന്നുകോ അധികം അപായമോ പഠനഫലമായി ഉണ്ടാകില്ലെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- ഈ പഠനത്തിന്റെ ഗവേഷകർ, നൈതീക കമ്മിറ്റി, നിയന്ത്രണാധികാരികൾ എന്നിവർക്ക് എന്റെ ആരോഗ്യവിവരങ്ങൾ ഞാൻ പഠനത്തിൽനിന്നും പിൻവാങ്ങിയാലും പരിശോധിക്കാൻ എന്റെ സമ്മതം അവശ്യമില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. ഇതിനു ഞാൻ സമ്മതിക്കുന്നു, [ ]
- ഭാവിയിൽ മൂന്നാം കക്ഷികൾക്കോ പ്രസിദ്ധീകരണത്തിനോ നൽകുമ്പോൾ എന്റെ വ്യക്തിവിവരങ്ങൾ വെളിപ്പെടുത്തുകയില്ലെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]

- സ്വമേധയാ പഠനത്തിൽ പങ്കെടുക്കാൻ ഞാൻ സമ്മതിക്കുന്നു. [ ]
- സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു പ്രതി എനിക്ക് കിട്ടി. [ ]

പേര് സാക്ഷിയുടെ പേര്

ഒപ്പ് ഒപ്പ്

തീയതി തീയതി

രോഗിയുമായുള്ള ബന്ധം

PROFORMA

Title: ASSESSMENT OF CAROTID PLAQUE VULNERABILITY USING 3TESLA MAGNETIC RESONANCE IMAGING AND ITS CORRELATION WITH CAROTID ENDARTERECTOMY SPECIMEN HISTOPATHOLOGY

1. Patient ID :
2. Age:
3. Sex :
4. CEA Side: Right/Left/ Bilateral
5. Date of CEA:
6. Date of MR plaque Imaging: Period between MR imaging and CEA:
7. Date of last cerebrovascular event:
8. NIHS score at the time of admission:
9. Total number of events before surgery:
10. Risk Factors:
    a) Smoker Yes / No
    b) Diabetes Mellitus Yes / No
    c) Alcoholic Yes / No
    d) Hypertension Yes / No
    e) Coronary Artery Disease Yes / No
    f) Dyslipidemia Yes / No
    g) Chronic Kidney Disease Yes / No
    h) Peripheral Artery Disease Yes / No
    i) Serum Cholesterol - LDL - HDL - Triglyceride -
11. Degree of stenosis in CTA :
12. Degree of stenosis in MRI :
13. 3T MRI Findings

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

Radiologist
a) T1W Hyper / Hypo / Iso
b) T2W Hyper / Hypo / Iso
c) PD Hyper / Hypo / Iso
d) TOF MRA

e) DWI Hyper / Not hyper
f) SWI Hypointense areas present/ Not present
g) Plaque Vulnerable/ Not vulnerable
h) Degree of stenosis in MR :
i) Thickness of fibrous cap: Not measurable / Measurable If so thickness=
j) Ulceration :

14. Histopathology findings

a) Calcification Present / Absent
b) Fibrous cap Intact / Ruptured.
c) IPH Present / Absent
d) Lipid Necrotic core Present / Absent

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 Filling

STUDY DATA SHEET

11	10	9	8	7	6	5	4	3	2	1	PATIENT ID
2	2	2	1	1	1	1	2	1	2	2	SEX
60	75	73	75	67	64	66	50	70	64	66	AGE
2	2	1	1	2	1	2	2	2	1	2	SIDE OF CEA
2	2	2	2	1	1	2	2	2	2	2	SMOKING
1	1	1	1	1	2	1	1	1	1	2	DM
2	2	2	2	2	1	2	2	2	2	2	ALCOHOLISM
1	1	2	1	1	2	1	1	2	1	1	HTN
2	2	2	2	2	2	2	2	2	2	2	CAD
1	2	2	1	1	2	2	2	2	2	2	DLP
207	111	127	139	91	75	70	114	155	131	129	SERUM CHOLESTEROL
133	59	78	75	44	54	50	70	86	69	71	LDL
116	121	122	93	69	80	73	150	121	139	117	TRIGLYCERIDE
35	43	40	55	36	40	26	33	46	44	49	HDL
2	2	2	2	2	1	2	2	2	2	2	POVD
2	2	2	2	2	2	2	2	2	2	2	CKD
0	0	0	0	0	0	2	1	8	0	0	NIHS AT ADMISSION
5	6	4	3	3	7	3	2	1	1	1	NO. OF EVENTS
33	174	0	66	17	121	3	86	34	26	25	NO. OF DAYS BETWEEN LAST EVENT & MRI
2	1	1	2	1	8	1	1	1	1	2	DAYS BETWEEN MR & CEA
73.8	80	68	79.6	73.5	74.6	78.8	75.3	72.1	72.3	76.2	MR STENOSIS
75.9	87	75	75	82.3			74.4	75.8	78.3	79.3	CT STENOSIS
1	2	1	1	1	2	2	2	1	2	2	IPH IN MRI
2	1	2	2	1	2	1	1	1	1	1	LIPID NECROSIS IN MRI
1	1	1	1	1	2	1	2	1	1	1	VULNERABILITY IN MRI
2	1	2	2	2	2	2	1	2	2	1	MRI FIBROUS CAP
2	1	2	1	2	1	2	2	2	1	1	CALCIFICATION IN MR
6.83E-04	8.77E-04	0.0012	5.26E-04	0.00102	8.54E-04	0.00109	4.11E-04	5.93E-04	0.00133	0.00185	ADC VALUE
3	3	3	3	3	3	1	1	2	3	3	CALCIFICATION IN HISTOLOGY
1	1	2	1	2	2	1	1	2	1	1	FIBROUS CAP IN HISTOLOGY
1	2	1	2	1	1	2	2	1	2	2	IPH IN HISTOLOGY
1	1	1	2	1	1	1	1	1	1	1	LIPID NECROSIS IN HISTOLOGY
1	1	1	1	1	1	1	1	1	1	1	VULNERABILITY IN HISTOLOGY

23	22	21	20	19	18	17	16	15	14	13	12	PATIENT ID
1	1	1	2	1	2	1	1	1	1	1	1	SEX
66	63	65	75	52	68	65	65	67	71	64	69	AGE
2	1	1	1	1	1	2	2	2	2	2	1	SIDE OF CEA
2	1	1	2	1	2	2	1	2	1	1	2	SMOKING
1	1	1	1	2	2	1	1	2	2	2	2	DM
2	2	1	2	1	2	2	1	1	2	1	2	ALCOHOLISM
1	1	1	1	1	1	1	1	1	1	1	1	HTN
2	2	2	2	2	2	2	2	2	2	2	2	CAD
1	2	1	2	1	2	1	1	1	1	2	1	DLP
128	70	110	93	121	194	60	109	122	160	158	70	SERUM CHOLESTEROL
79	50	72	42	66	113	30	52	77	94	85	50	LDL
83	73	112	116	100	54	98	149	69	311	95	73	TRIGLYCERIDE
41	26	45	44	46	69	24	27	41	28	54	26	HDL
2	2	2	2	2	2	2	2	2	1	2	2	POVD
2	2	2	2	2	2	2	2	2	2	2	2	CKD
0	0	6	0	2	1	0	3	3	0	0	1	NIHS AT ADMISSION
1	0	2	3	1	1	6	1	1	1	3	1	NO. OF EVENTS
14		11	87	148	18	22	10	49	31	16	274	NO. OF DAYS BETWEEN LAST EVENT & MRI
50	1	21	2	1	1	1	1	1	1	2	1	DAYS BETWEEN MR & CEA
72.9	57.9	76.9	75	73.2	62	73	86	82	68.8	71.9	76.9	MR STENOSIS
72.7	60		78.2	84.2		77	84		77.8	73	85	CT STENOSIS
2	2	2	2	2	2	2	1	1	2	1	1	IPH IN MRI
2	2	2	2	1	2	2	2	2	1	2	2	LIPID NECROSIS IN MRI
2	2	2	2	1	2	2	1	1	1	1	1	VULNERABILITY IN MRI
2	2	1	2	2	2	1	2	2	2	2	2	MRI FIBROUS CAP
1	1	1	1	1	1	1	2	2	2	1	2	CALCIFICATION IN MR
0.00254	7.17E-04	0.00129	0.00254	0.00107	0.00254	0.00161	8.34E-04	7.81E-04	5.49E-04	7.98E-04	1.05E-09	ADC VALUE
2	3	3	3	3	2	3	2	1	1	3	3	CALCIFICATION IN HISTOLOGY
1	1	1	1	1	1	1	2	2	2	1	2	FIBROUS CAP IN HISTOLOGY
2	2	2	2	2	2	2	1	1	2	1	1	IPH IN HISTOLOGY
2	2	2	2	2	2	2	2	2	1	1	1	LIPID NECROSIS IN HISTOLOGY
2	2	2	2	2	2	2	1	1	1	1	1	VULNERABILITY IN HISTOLOGY

KEY TO DATA SHEET

1.	**SEX**	1 -Male	2	-Female
2.	**SIDE OF CEA**	1 -Right	2	-Left
3.	**SMOKING**	1 -Present	2	-Absent
4.	**DM(Diabetes Mellitus)**	1 -Present	2	-Absent
5.	**ALCOHOLISM**	1 -Present	2	-Absent
6.	**HTN(Hypertension)**	1 -Present	2	-Absent
7.	**CAD(Coroanry Artery Disease)**	1 -Present	2	-Absent
8.	**DLP(Dyslipidemia)**	1 -Present	2	-Absent
9.	**POVD(Peripheral occlusive vascular disease)**	1 -Present	2	-Absent
10.	**CKD(Chronic Kidney Disease)**	1 -Present	2	-Absent
11.	**IPH IN MRI(Intraplaque Hemorrhage)**	1 -Present	2	-Absent
12.	**LIPID NECROSIS IN MRI**	1 -Present	2	-Absent
13.	**VULNERABILITY IN MRI**	1 -Vulnerable	2	-Non- vulnerable
14.	**MRI FIBROUS CAP**	1 -Intact	2	-Ruptured
15.	**CALCIFICATION IN MR**	1 -Present	2	-Absent
16.	**CALCIFICATION IN HISTOLOGY**	1 -Present	2	-Absent
17.	**FIBROUS CAP IN HISTOLOGY**	1 -Intact	2	-Ruptured
18.	**IPH IN HISTOLOGY(Intraplaque Hemorrhage)**	1 -Present	2	-Absent
19.	**LIPID NECROSIS IN HISTOLOGY**	1 -Present	2	-Absent
20.	**VULNERABILITY IN HISTOLOGY**	1 -Vulnerable	2	-Non- vulnerable

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1239/AUGUST-2018

28.08.2018

Dr. Ajay Alex
Senior Resident
Department of IS & IR
SCTIMST, Thiruvananthapuram

Dear Dr. Ajay Alex,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "ASSESSMENT OF CAROTID PLAQUE VULNERABILITY USING 3TESLA MAGNETIC RESONANCE IMAGING AND ITS CORRELATION WITH CAROTID ENDARTERECTOMY SPECIMEN HISTOPATHOLOGY (IEC/1239)" on 17th August, 2018.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Forwarding Letter from the HOD*
6. *Proforma*
7. *Information Sheet and Consent Form in English and Malayalam*
8. *CV of Principal Investigator and Co- Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 23.08.2018 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Forwarding Letter from the HOD*
6. *Proforma*
7. *Information Sheet and Consent Form in English and Malayalam*
8. *CV of Principal Investigator and Co- Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 17th August, 2018 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
3.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
4.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
5.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

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,

Mala Ramanathan
Member Secretary, IEC

PLAGIARISM ANALYSIS REPORT

(Urkund)

URKUND

Document Information

Analyzed document	CAROTID PLAQUE THESIS DRAFT WITHOUT reference.docx (D78202854)
Submitted	8/26/2020 5:31:00 PM
Submitted by	ANOOP AYYAPPAN
Submitter email	anoop.a@sctimst.ac.in
Similarity	5%
Analysis address	anoop.a.sctims@analysis.urkund.com

Sources included in the report

SA	**CAROTID PLAQUE THESIS 2018 corrrected.docx** Document CAROTID PLAQUE THESIS 2018 corrrected.docx (D37966060)	8
SA	**Arunprabu Final Thesis.docx** Document Arunprabu Final Thesis.docx (D31320732)	3
W	URL: https://link.springer.com/content/pdf/10.1007%252F978-3-211-32509-4.pdf Fetched: 8/26/2020 5:47:00 PM	4
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4706840/ Fetched: 8/26/2020 5:47:00 PM	8
W	URL: https://www.researchgate.net/publication/7829408_Ultrasound_Measurement_of_the_Fib ... Fetched: 10/16/2019 10:41:32 AM	1
W	URL: https://www.sciencedirect.com/science/article/pii/S0741521404005749 Fetched: 8/26/2020 5:47:00 PM	1
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3004802/ Fetched: 8/26/2020 5:47:00 PM	1
W	URL: https://thejns.org/focus/view/journals/neurosurg-focus/36/1/article-pE1.xml Fetched: 8/26/2020 5:47:00 PM	1
W	URL: https://www.researchgate.net/publication/255177380_Imaging_of_the_Carotid_Artery_V ... Fetched: 4/6/2020 9:22:23 AM	2
SA	**Arunprabu Plagiarism.docx** Document Arunprabu Plagiarism.docx (D31194636)	1
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3504380/ Fetched: 12/19/2019 9:41:00 PM	1