SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM, KERALA



"THE COMPARISON OF HIGH-RISK PLAQUE FEATURES IN ASYMPTOMATIC AND SYMPTOMATIC CAROTID STENOSIS BY MAGNETIC RESONANCE CAROTID PLAQUE IMAGING"

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and regulations for Post-Doctoral Fellowship in Stroke

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DECLARATION BY THE STUDENT

I, **Dr. Poornima Nair,** hereby certify that I had personally carried out the work depicted in the thesis titled, **— The Comparison Of High-Risk Plaque Features In Asymptomatic And Symptomatic Carotid Stenosis By Magnetic Resonance Carotid Plaque Imaging .** No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.



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Date: 31-12-2024

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This is to certify that the dissertation entitled '**The Comparison Of High-Risk Plaque Features In Asymptomatic And Symptomatic Carotid Stenosis By Magnetic Resonance Carotid Plaque Imaging'** is a bonafide research work done by **Dr Poornima Nair ,** Post doctoral fellow in Department of Neurology, in partial fulfillment of the requirement of Postdoctoral fellowship in Stroke .



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Chapter 1

Introduction

INTRODUCTION

Carotid artery atherosclerosis is a major contributor to ischemic strokes, responsible for up to 20% of strokes and TIAs. The presence of carotid artery plaque, its characteristics and features have been extensively studied.

The degree of carotid artery stenosis is known to be strongly associated with stroke risk in symptomatic patients with carotid atherosclerotic disease.[1] It is becoming increasingly apparent that the acute disruption of atherosclerotic plaques precedes the onset of clinical syndromes.[2] Unstable plaques, characterized by cap rupture, leads to thromboembolism and stroke.

Asymptomatic carotid artery stenosis (aCAS) is defined as stenosis of extracranial carotid arteries without a history of ipsilateral ischemic stroke or transient ischemic attack. The estimated prevalence of severe aCAS (≥70%) increases with age and ranges from 0.1% to 3.1% with a population- attributable stroke risk of 0.7%.[3]

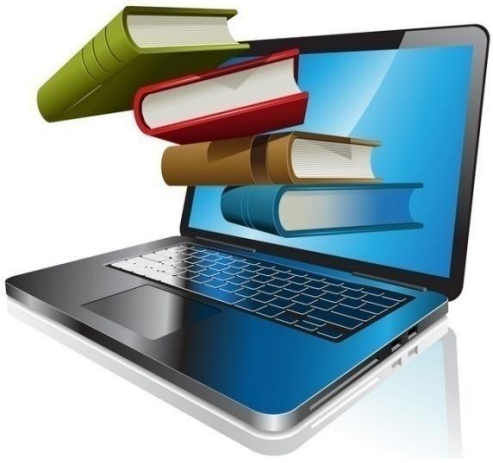
ACAS found a 5-year risk of ipsilateral stroke, perioperative stroke, or death of 5.1% vs 11.0% in the CEA vs BMT arm.[4] ACST-1 found a 5-year risk of stroke and perioperative events of 6.4% vs 11.8% in the CEA vs BMT arm. [5] The 5-year ipsilateral stroke risks in the medical arm of the 1995 ACAS trial and the 2010 ACST-1 were 11% and 3.6%, respectively.[6] The 2011 AHA guidelines recommend CEA in patients with aCAS with ≥70% stenosis if perioperative stroke, myocardial infarction, and death rates are low.[7] The high risk plaque features include intraplaque hemorrhage, large lipid-rich necrotic core, thin or ruptured fibrous cap, plaque irregularity, silent embolic infarcts, progression, ulceration, echolucency, mural thrombus, neovascularization, inflammation, large juxta-liminal hypoechoic area, large plaque volume, microembolic signals, and impaired cerebrovascular reserve .[8] A recent meta analysis quotes the

pooled prevalence of high-risk plaques to be 26.5% & the associated risk of an ipsilateral ischemic cerebrovascular event higher than those without high risk features.(4.3 v/s 1.2 per 100 person years).[9]

This study aims to compare the high risk plaque features in symptomatic and asymptomatic carotid artery stenosis with carotid plaque imaging

Chapter 2

Review of Literature



Atherosclerotic carotid artery plaque

Carotid atherosclerotic plaque most commonly occurs at the bifurcation of CCA and in the carotid bulb. There are several modifiable and non modifiable risk factors like high blood pressure, smoking, elevated low density lipoproteins, uncontrolled diabetes and ethnicity which contributes to carotid atherosclerosis. But hydrodynamic factors like low wall shear stress and resultant flow stagnation appear to be important. The combination of low wall shearstress, hypercholesterolemia and turbulent blood flow contribute to the development of plaque. The so-called 'vulnerable plaque' is characterized by the presence of a lipid-rich necrotic core (LRNC) that is covered by thin fibrous cap and few smooth muscle cells.[10,11] Atherosclerosis is initiated by the entry of LDL particles into the subintimal space and gets trapped into the glycoprotein complexes at the site., which soon gets oxidized under optimal metabolic conditions. This activates monocytes and smooth muscle cells into the site that initiate local inflammation. Monocytes gets converted to macrophages, that engulfs the lipids and transforms into foam cells.[12.] When these cells die, free cholesterol is released into the extracellular space, which attracts more macrophages to the site , leading to a vicious cycle. This forms a necrotic core rich in cellular debris and cholesterol. The initial cholestersol clefts gets transformed into crystals . This change from liquid to solid state expands the volume of the plaque. This stretches the fibrous cap, which progressively becomes thinner. The fibrous cap finally ruptures , leading to separation of the core from the lumen. This causes either artery to artery embolization , or distal luminal obstruction. perorating crystals [13]

<u>The fibrous cap</u>

Fibrous cap maintains the integrity of the plaque. It is composed of collagen fibres -type 1 and 3 ,

along with smooth muscles embedded in extracellular matrix. Its included in type 4 atheromatous lesions according to the American Heart Association classification. Symptomatic carotid stenosis is often associated with type 5 or 6 plaques. Type 5 and 6 are the complex plaques with vulnerable features like ulceration, thrombus and intraplaque hemorrhage.[14] Thinning of the fibrous cap or cap rupture is an independent risk factor for ischemic neurological symptoms. Fibrous cap thinning ranges from 74—95% in symptomatic and 32-48% in asymptomatic plaques.[15] The action of metalloproteinases released by macrophages causes autolysis of the cap and releases the plaque material to embolize. Moreover, the fibrous cap can be thinned by stretching when the LRNC undergoes volume expansion during crystallization.[12]

Lipid-rich necrotic core

A large lipid core is the most important factor of a vulnerable plaque. Its representative of the accumulated cholesterol in the arterial wall. [16,17] Cholesterol rich core is the major trigger for crystallization, which leads to volume expansion and later plaque rupture.

MR plaque imaging can detect large lipid cores, which is useful in detecting vulnerable plaques.[18] Contrast enhanced Ultrasound can detect plaque echolucency, ulceration, volume of the plaque and the flow patterns which decides the plaque vulnerability.

A larger LRNC is associated with thin or ruptured fibrous cap in both symptomatic and asymptomatic carotid atherosclerotic disease. The volume of LRNC is a strong predictor of future surface disruption in asymptomatic moderate stenosis.[19] Furthermore, a larger LRNC provides an environment that is conducive to macrophage activation, which releases proteolytic enzymes that degrade collagen. Furthermore, several tissue factors are found in the necrotic core that when exposed to blood can lead to acute thrombosis, embolization and stroke .[20]

Moreover, tearing of the plaque cap causes the cholesterol crystals to be aligned in parallel formation, which in turn increases the pressure within the plaque causing it to rupture.[21]

Inflammatory cell infiltrate

Symptomatic patients have an increased percentage of inflammatory infiltrate composed of T lymphocytes and macrophages as compared to asymptomatic patients.[22,2] Macrophages produce matrix metalloproteinases that breakdown the collagen. T cells induce the secretion of matrix metallo proteases and secrete IFN-γ, that results in impaired collagen synthesis.[24]

All these result in fibrous cap rupture.

Cholesterol droplets within the plaque activates NLRP3 and IL- 1 Beta to cause production of CRP. There is a strong association between the neutrophils and vulnerable plaques and is associated with a large lipid rich necrotic core. [25]

Intraplaque hemorrhage (IPH)

Most mature plaques have a rich supply of small vessels, called as '*vasa vasorum*', that interweave into the plaque matrix.[26,27] IPH predicts the future risk of neurological events. Carr *et al*. showed that IPH was more prevalent in symptomatic patients as compared to asymptomatic patients (84 vs 56% asymptomatic patients; $p = 0.06$). There was strong correlation between IPH and plaque rupture. Symptomatic moderate stenosis had higher prevalence of IPH than mild stenosis.[15]

Repeated IPH increases the cholesterol content in LRNC.[28] Hence IPH plays an important role in necrotic core growth.

Factors influencing plaque morphology

- **Age-** Oxford plaque study looked into the characteristics of 526 carotid endarterectomy (CEA) specimens. They found that younger patients had a greater proportion of inflammatory cell infiltration and older patients had a large lipid core and plaque calcification, but there was no age-related trend towards plaque instability.[29]
- **Gender-**. In asymptomatic patients with moderate stenosis (>50%) high-risk plaque features were more prevalent in men than in women. [30] Men had thinner fibrous caps and larger LRNC for the same degree of stenosis. Larger LRNC are more likely to rupture while smaller LRNC are more likely to erode. [31]

Smoking

Smoking accelerates the progression of atherosclersosis. However, morphology of plaque is similar in ex smokers and never smokers, which may explain that plaque instability may be unrelated to smoking. [29] However, physiological plaque alterations cannot be ruled out.

Timing of ischemic symptoms

Plaque instability relates to nature and timing of ischemic events. The Oxford plaque study showed that plaque instability may persist after a transient ischemic attack (TIA) and then decreases with time after a stroke. Plaques removed 180 days after an event had greater inflammation and was more vulnerable than after a TIA.[29] As time lapses, there is decrease in the number of macrophages and reduced expression of IL6 , caspase and Il -8 , making the plaque to become more stable. [32]

Imaging of carotid artery stenosis

There are a number of non-invasive and invasive imaging modalities to study carotid plaque, which include Doppler-ultrasound; transcranial Doppler (TCD); computer tomographic angiography (CTA); and MRI; - plaque imaging and positron emission tomography (PET).

Ultrasound

High-resolution (<0.4 mm axial), gray-scale, real-time B-mode ultrasound with

Doppler flow imaging is utilized to image carotid arteries.

Due to overall low prevalence of asymptomatic carotid stenosis, routine ultrasound in general asymptomatic population is not recommended. [33] Doppler ultrasound must be used in patients with signs and symptoms of retinal and/or cerebral ischemia and patients who have a carotid bruit on physical examination.[34] Doppler can also identify plaques at high risk of embolization.[35] The major limitation is that its user dependent. The presence of plaque echolucency, ulceration, plaque irregularity can be made out using doppler. It helps in assessment of intimal medial thickness and the percentage of stenosis in symptomatic carotid patients.

Magnetic resonance imaging

High-resolution MR plaque imaging is widely used to evaluate characteristics of atherosclerosis. The presence of IPH, LRNC and thinning of the fibrous cap have been validated by histological correlation . [36,37,38] These high risk plaque features favours plaque rupture with subsequent ischemic events. The significance of the plaque imaging high risk features have been confirmed in studies of asymptomatic patients with moderate carotid stenosis. [39,40]

In a subset of patients enrolled in the Trial of ORG 10172 in Acute Stroke Treatment(TOAST) who had severe ipsilateral carotid stenosis, the presence of IPH showed a higher incidence of repeat ischemic events in the followup period of 9 months as compared to patients without IPH. (18.7 vs 3%; p = 0.051). [41] IPH was also associated with spontaneous microembolic activity by TCD Imaging. [42] Thus plaque MRI has shown to identify features beyond luminal stenosis that predict risk of TIA and stroke. Data shows that patients with LRNC with or without IPH may represent the desired phenotype of patients for monitoring treatment effects. [43]

Thus, carotid plaque MRI may guide in monitoring changes in high risk carotid plaque and well as to decide on future therapeutic strategies

Computed tomography angiography (CTA)

CTA is one of the most accurate methods to evaluate the plaque characteristics. Compared with conventional CTA, dual-energy CTA has better accuracy in identifying the vulnerable plaque features with greater accuracy.[44] The evaluation of degree of carotid stenosis using CTA has been extensively studied. CTA is comparable to catheter angiography for evaluation of extracranial vascular disease, with specificity ranging from 63 to 100% and sensitivity 65 to 100% . CTA often underestimates the degree of stenosis , needing careful assessment. [45].

Transcranial Doppler ultrasound(TCD)

Transcranial Doppler ultrasound is used to detect both intra- and extracranial arterial disease. TCD helps to assess the hemodynamic effects on intracranial circulation of carotid artery stenosis. The flow velocity in the intracranial circulation is often reduced depending upon on the severity of carotid artery stenosis.[46] TCD is used to look for the presence of micro embolic

signals in patients with carotid artery stenosis, which may independently predict acute stroke risk, recurrence, symptomatic carotid lesion and also postoperatively after carotid endarterectomy. Embolic signals are more frequent in patients with large artery disease and minimal absent in lacunar stroke. This can be used to determine the stroke etiology and identify patients at risk for further ischemic events who require more aggressive antiplatelet therapy. The Asymptomatic Carotid Emboli Study (ACES) concluded that embolic signals in asymptomatic carotid stenosis were associated with higher risk of stroke and TIA.[47] Hence it is possible that asymptomatic patients may benefit from carotid revascularization. In a study which conducted simultaneous carotid ultrasound and TCD

in possible unstable plaques, showed the release of particulate materials, likely cholesterol crystals, during the test by even the gently manipulation of the ultrasound probe over carotid artery. [48]

Serum biomarkers & carotid artery plaque

Serum biomarkers reflecting molecular processes like inflammation, apoptosis, lipid accumulation, thrombosis and proteolysis is highly related to plaque vulnerability and may help distinguish stable and unstable plaques. plaques. Serum biomarkers are mainly inflammatory and proteolytic markers like the high-sensitivity Creactive protein, , MMP-2, IL-6, MMP-9 , tissue inhibitors of metalloproteinases (TIMP)-1 and -2. This non-invasive way helps to identify high-risk patients in the future who can benefit from carotid surgery. In addition, the use of combination of biomarkers along with imaging findings (fluordeoxyglucose uptake by PET/CT scanning) may provide new insights into plaque instability[49].

The understanding the high risk plaque features in MRI is growing for the past few decades. In 2002, Cai et al. used multispectral MRI to identify high risk features, like (IPH), lipid-rich necrotic core (LRNC), and fibrous cap rupture. On follow-up at 38 months of these patients , they found that plaques with IPH, larger lipid necrotic core , thin or ruptured fibrous cap, and maximum wall thickness were associated with subsequent cerebrovascular events. Their pilot study with 32 patients showed that one-third of patients with cryptogenic stroke had complex, nonstenotic plaques, with IPH as the mostcommon finding.[50]

Asymptomatic carotid artery stenosis (aCAS).

The estimated prevalence of severe aCAS (≥70%) increases with age and ranges from 0.1% to 3.1% in age <50 to those age > 80, with a population- attributable stroke risk of 0.7%. [1]

ACS is a marker of generalized atherosclerosis in other vascular beds. [5] Patients with ACS and vulnerable plaque are at higher risk of ipsilateral stroke and TIA. [52]

Patients with aCAS who had high-risk plaques had a summary odds ratio of 3.0 (95% CI, 2.1–4.3) for ipsilateral ischemic cerebrovascular events, compared with patients without such plaques. Such patients have an incidence rate of 4.3% per year for combined ipsilateral stroke or TIA.[9] One of the most discriminating features in ACS is the presence of microemboli on transcranial Doppler monitoring (summary odds ratio, 5.6 [95% CI, 2.0–15.3] for ipsilateral events).

In a study of 319 patients with ACS who underwent transcranial Doppler embolus detection, patients with microemboli were much more likely to have a stroke during the first year of follow-

up than those without microemboli (15.6% versus 1%, respectively;*P*<0.00001).[53]

This study aims to estimate the prevalenceand compare the high risk plaque features in asymptomatic and symptomatic moderate to severe carotid artery stenosis using MR carotid plaque imaging

Chapter 3

Aims &Objectives



AIMS AND OBJECTIVES

Objectives:

- To estimate the prevalence of high risk plaque features in asymptomatic and symptomatic moderate to severe carotid artery stenosis using MR carotid plaque imaging.
- To compare the high risk plaque features in asymptomatic and symptomatic carotid stenosis

Chapter 4

Materials &Methods



MATERIALS AND METHODS

Study design: Prospective single centre study

Study setting: In-patient and Out-patient blocks of Neurology Department of Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram

Study Population: All patients with symptomatic and asymptomatic carotid artery stenosis who present to Stroke OPD/ Stroke ICU of the comprehensive stroke care centre, SCTIMST satisfying the inclusion criteria will be included in the study.

Inclusion criteria: All patients who have symptomatic and asymptomatic carotid stenosis ≥50% on vascular imaging (CTA/ MRA).

The following asymptomatic patients were included in the study

1. Patients who undergo vascular imaging as pre procedure evaluation for CABG/ any other cardiac procedure.
2. Patients with asymptomatic carotid artery stenosis of ≥50% opposite to the side of the stroke
3. Patients who are screened for any other disease and detected to have asymptomatic carotid artery stenosis ≥50%

Exclusion criteria:

1. Patients with previous history of stroke / TIA in the same territory within 6 months
2. Patients with a proven cause for ischemic stroke like vasculitis, dissection.
3. Patients with baseline Modified Rankin scale (mrs ≥3)
4. Patients with preexisting renal dysfunction
5. Patients who have contraindication for undergoing MRI

Methodology

The study population included symptomatic carotid stenosis (>/=50%) and asymptomatic carotid stenosis (>/=50%) patients.

Symptomatic carotid stenosis patients were graded as moderate (50-69%) and severe (>70%) as per vascular imaging (CTA or MRA). Symptomatic carotid stenosis included those with transient ischemic attacks or strokes with focal neurological symptoms such as visual or speech disturbances, cranial nerve deficits, weakness, sensory or balance disturbances either due to embolic phenomenon or hypoperfusion related ischemic insults secondary to the carotid stenosis. Symptomatic patients who underwent MR carotid plaque imaging prior to CEA were included in the study.

Patients who undergo vascular imaging as pre procedure evaluation for CABG/ any other cardiac procedure and found to have >/=50% carotid stenosis, patients who present with stroke and have asymptomatic carotid artery stenosis ≥50% on the opposite side, patients who are screened for

any other disease and detected to have asymptomatic carotid artery stenosis ≥50% were recruited to the study. All these patients who have asymptomatic >/=50% stenosis in vascular imaging (CTA or MRA) underwent MR carotid plaque imaging.

Ischemic lesions were identified by MR Diffusion weighted imaging or non-contrast CT brain at the time of evaluation of the carotid stenosis. Multiple small cortical infarcts in ICA territory, territorial infarcts with or without fragmentation were classified as embolic pattern while infarcts in superficial and deep border zone areas were classified as hypoperfusion related, as published previously. Chronic and silent ischemic infarcts were identified using NCCT brain and FLAIR images. Small vessel ischemic changes were graded using the Fazeka grading system as grade 1 to 3.

From the previous studies [7] ,the prevalence of the most important high risk

features such as intraplaque hemorrhage and ulceration in asymptomatic carotid artery stenosis was found to be 16%, hence a sample size of 50 was calculated . The maximum attainable sample size was achieved, total of 46 asymptomatic carotids and 65 symptomatic carotids were included in the study.

.Each patient had a CT angiogram and/ or MR angiogram. . The severity of the stenosis was calculated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET)criteria . The severity of stenosis was classified as moderate (50-69%) and severe >/=70%. The presence of intracranial atherosclerotic disease was looked and the vessel and the percentage of stenosis was identified.

All clinical data were collected by direct patient interviews during admission and from electronic medical records.. Risk factors evaluated included diabetes mellitus, hypertension,

coronary heart disease, dyslipidaemia, renal disease, peripheral vascular disease, prior cerebral

ischemic events, prior antiplatelet use before the event, stroke severity (symptomatic carotid patients) , alcohol and tobacco use,antihypertensives and oral hypoglycemic agent use. Magnetic resonance imaging data for the study was extracted from Picture Archiving and Communication System (PACS), anonymized, and separated into numbered files. MR plaque images were then analyzed by a vascular radiologist with 5 years of experience in interpreting diagnostic vascular imaging studies who was blinded to clinical data and other imaging studies. Each MR image was assigned an image quality grade from 1 to 4, with 1 denoting poor image quality and 4 denoting outstanding image quality.

The analysis excluded studies (2 patients) with overall image quality ratings of 1 and 2. The images were independently analyzed to evaluate specific parameters, including the signal intensities of the carotid plaque, which were compared relative to the ipsilateral sternocleidomastoid muscle as shown previously. All eligible patients who were recruited provided written informed consent and the study was approved by the Institutional Ethics Committee (SCT/IEC 2216)

MR Plaque maging protocol

Carotid Plaque MR imaging was done using a General Electric Discovery 750E 3.0 Tesla machine equipped with a 6-channel carotid coil. Before placing the patient in the MR scanner, ultrasonography was employed to mark the level of maximum carotid stenosis on the skin.

This pre-scan marking ensured optimal positioning of the carotid surface coil, resulting in better signal quality. A standardized carotid plaque protocol was followed to obtain images of the carotid vessel, which included the following sequences: Three-dimensional (3D) time of flight (TOF) sequence (TR: 25, TE: 6, FOV: 15 x 15, matrix size: 320 x 224, section thickness: 1.2

mm, pixel size: 0.6 x 0.9); Axial Fast spin echo (FSE) T1-weighted imaging (T1WI) (FOV: 12 x 12, matrix size: 320 x 192, section thickness: 2 mm, pixel size: 0.4 x 0.6); Axial fast spin Echo (FSE) T2-weighted imaging (T2WI)(FOV: 12 x 12, matrix size: 256 x 192, section thickness: 2 mm, pixel size: 0.5 x 0.6); Axial fast spin Echo FSE proton density-weighted imaging (PDWI) (FOV: 12 x 12, matrix size: 256 x 192, section thickness: 2 mm, pixel size: 0.5 x 0.6); Axial FSE T2 weighted sequence with fat suppression (T2 FS) was used to better delineate plaque borders (FOV 12 X 12, matrix size: 256 x 192, section thickness: 2 mm, pixel size: 0.5 x 0.6). Pre- and post-contrast CUBE T1 with fat suppression (field of view: 16 x 16 mm, matrix size: 192 x 192 section thickness: 0.7 mm, pixel size: 0.8 x 0.8) was utilized to measure the amount of neo-vascularization and the continuity of the fibrous cap within the plaque. All images were acquired in the transverse plane,

except for the CUBE sequences, which were performed in the sagittal plane and centered to include the carotid bifurcation on the affected side. The regions of carotid stenosis were identified using rapidscreening TOF MRA, which evaluated the middle 15 cm of the neck. In order to retain clinically acceptable acquisition times while ensuring robustness against spontaneous patient movements, a typical diffusionweighted echo-planar sequence was used in this study. Additionally, T2, T2 FS, PD, and CUBE T1 sequences were processed using the zerointerpolation

technique (ZIP). The GE advantage workstation was utilized to independently analyze the images. The dominating element of the plaque and the existence of multiple high-risk features were tabulated during the image analysis process in descending order of their occurrence within the plaque. The atherosclerotic plaques were classifie using the modified AHA classification for comparison .

The high risk plaque features studied in MR carotid plaque imaging included the presence of intraplaque hemorrhage , lipid rich necrotic core, ruptured fibrous plaque, ulcerated plaque , plaque irregularity, presence of mural thrombus in the descending order of frequency as per prior studies. A high risk plaque was defined as having any of the above features in isolation or combination . Low risk plaque features included absence of IPH, fibrous or calcium rich plaque, with intact fibrous cap without ulceration or plaque irregularity or mural thrombus. A low risk plaque was defined as having any of the above features in isolation or combination.

LRNC appears mildly hypo- to mildly hyperintense to adjacent musculature on fat-suppressed T1- weighted images, slightly hypointense to adjacent muscle on MPRAGE images and do not enhance on contrast-enhanced images.IPH is typically intense hyperintense in TOF angio and T1 weighted images with no post contrast enhancement. Ulceration was defined as cavitation into the plaque measuring atleast 1-2 mm . A fibrous cap is located along the surface of a plaque and is typically hypointense on TOF images, isointense on T1 and T2, and enhances on postcontrast images.Intact/thick FC appears as a continuous hypointense band near the bright lumen on 3D-TOF images, and a smooth luminal surface. Plaques where the hypointense band could not be visualized were categorized as having an intact/thin FC. FC rupture was identified by the absence or discontinuity of the hypointense band, juxtaluminal hyperintense signal in the TOF and T1-weighted (T1W) images (consistent with recent hemorrhage), and/or an irregular lumen surface. Neovascularisation is a surrogate of plaque enhacement and is identified as enhancement in post contrast images. Calcifications are markedly hypointense on all sequences & described as having “jet black” in appearance.

The high risk plaque features were analysed in asymptomatic carotid stenosis and compared

with the high risk plaque features in symptomatic carotid stenosis .

Statistical analysis

Continuous variables were presented as mean ± 1 standard deviation

(SD) ranges. Chi-square test was used for categorical variables and T test was used for continuous variables. To evaluate the quantification of stenosis using MR and CT,

the Pearson correlation test was conducted. A p-value < 0.001 was considered indicative of a significant difference. The prevalence of high risk plaque features were analyzed using Statistical analysis was performed using IBM SPSS 23 analysis software. There was no funding source for this study.

Chapter 5

Results



RESULTS

Of the total 73 patients, 39 patients had both symptomatic and asymptomatic carotids, 26 patients had only symptomatic carotids and 8 had only asymptomatic carotids. Thus there were total of 111 carotids, 46 symptomatic and 65 symptomatic.

Five asymptomatic patients underwent plaque imaging 1 year post CEA on the opposite side, 32 symptomatic patients underwent CEA & 2 asymptomatic patients had underwent CEA .

After excluding poor quality images (2) and post endarterectomy status(5), there were a total of 44 asymptomatic carotids and 58 symptomatic carotids with MR carotid plaque imaging

. The mean age was 64.1 +/- 6.75 years and majority were males (85/111, 76.5%). The most common risk factors were hypertension (84/111; 75.6%) and diabetes (81/111; 72.9%).

Table 1 - The baseline demographic and clinical profiles in both the study groups.

				Chi-square	p value
		Asymptomatic(46)	Symptomatic(65)		
	Left	18 (39.1%)	37 (56.9%)	3.411[a]	0.065
	Right	28 (60.9%)	28 (43.1%)		
Percentage of stenosis	50-69	18 (39.1%)	15 (23.1%)	3.323[a]	0.068
	>=70	28 (60.9%)	**50 (76.9%)**		
Sex	Male	33 (71.7%)	52 (80%)	1.025[a]	0.311
	Female	13 (28.3%)	13 (20%)		
Diabetes	Yes	32 (69.6%)	49 (75.4%)	.463[a]	0.496
	No	14 (30.4%)	16 (24.6%)		
Hypertension	Yes	33 (71.7%)	51 (78.5%)	.661[a]	0.416
	No	13 (28.3%)	14 (21.5%)		

Dyslipidemia	Yes	25 (54.3%)	35 (53.8%)	.003[a]	0.958
	No	21 (45.7%)	30 (46.2%)		
Atrial Fibrillation	Yes	1 (2.2%)	1 (1.5%)	.061[a]	0.804
	No	45 (97.8%)	64 (98.5%)		
Coronary artery disease	Yes	12 (26.1%)	15 (23.1%)	.133[a]	0.716
	No	34 (73.9%)	50 (76.9%)		

Stroke was the most common presentation in the symptomatic group.

Table 2: Baseline characteristics in the study population

Antiplatelet	**Yes**	**12 (26.1%)**	**20 (30.8%)**	**32**	**.288[a]**	**0.592**
	No	**34 (73.9%)**	**45 (69.2%)**	**79**		
Single antiplatelet	**Yes**	**11 (91.7%)**	**19 (95%)**	**30**	**.142[a]**	**0.706**
	No	**1 (8.3%)**	**1 (5%)**	**2**		
Dual antiplatelet	**Yes**	**7 (58.3%)**	**8 (40%)**	**15**	**1.012[a]**	**0.314**
	No	**5 (41.7%)**	**12 (60%)**	**17**		
Antihypertensives	**Yes**	**33 (71.7%)**	**51 (78.5%)**	**84**	**.661[a]**	**0.416**
	No	**13 (28.3%)**	**14 (21.5%)**	**27**		
Anticoagulants	**Yes**	**2 (4.3%)**	**1 (1.5%)**	**3**	**.808[a]**	**0.369**
	No	**44 (95.7%)**	**64 (98.5%)**	**108**		
Statins	**Yes**	**26 (56.5%)**	**37 (56.9%)**	**63**	**.002[a]**	**0.966**
	No	**20 (43.5%)**	**28 (43.1%)**	**48**		

None of the high-risk plaques were associated with the age or severity of stenosis in study population.

Table 3- Baseline characteristics in the study population

TIA	Yes	0 (0%)	28 (43.1%)	28	26.500[a]	0.000
	No	46 (100%)	37 (56.9%)	83		
Territory	Hemispheric	23 (82.1%)	(0%)	23		
	Retinal	4 (14.3%)	(0%)	4		
	Both	1 (3.6%)	(0%)	1		
Stroke	Yes	0 (0%)	45 (69.2%)	45	53.559[a]	0.000
	No	46 (100%)	20 (30.8%)	66		
Side	Left	24 (53.3%)	(0%)	24		
	Right	20 (44.4%)	(0%)	20		
	Both	1 (2.2%)	(0%)	1		
Territory_stroke	Hemispheric	42 (93.3%)	(0%)	42		
	Retinal	2 (4.4%)	(0%)	2		
	Both	1 (2.2%)	(0%)	1		
CEA	Done	2 (4.3%)	57 (87.7%)	59	75.144[a]	0.000
	Not done	44 (95.7%)	8 (12.3%)	52		
Total		46 (100%)	65 (100%)	111		
Chronic Infarct	Yes	17 (37%)	21 (32.3%)	38	.259[a]	0.611
	No	29 (63%)	44 (67.7%)	73		
Ipsi_contra	Ipsilataral	6 (35.3%)	18 (85.7%)	24	10.264[a]	0.001
	Contralataral	11 (64.7%)	3 (14.3%)	14		
Infarct location	Cortical	3 (17.6%)	3 (14.3%)	6	1.597[a]	0.450
	Subcortical	12 (70.6%)	12 (57.1%)	24		
	Both	2 (11.8%)	6 (28.6%)	8		

17 amongst 46 asymptomatic carotids had chronic infarcts in CT, with majority being subcortical (70.6% 12/17). 6 (35.3%) had chronic infarcts ipsilateral to the side of asymptomatic carotid stenosis and 11 (64.7%) on the opposite side. Similar findings were noted in MRI. Most patients in asymptomatic group (65.9%) and symptomatic group (81.4%) had severe stenosis (≥70 %).

Table 4- Characteristics in CT angiogram in the study population

CT angiogram	Yes	41 (89.1%)	59 (90.8%)		
	No	5 (10.9%)	6 (9.2%)		
Severity of stenosis	50-69	14 (34.1%)	11 (18.6%)	3.100[a]	0.078
	>=70	27 (65.9%)	48 (81.4%)		
Ulceration	Yes	5 (23.8%)	14 (23.7%)	.000[a]	0.994
	No	16 (76.2%)	45 (76.3%)		
Thrombus	Yes	0 (0%)	1 (1.7%)	.702[a]	0.402
	No	41 (100%)	58 (98.3%)		
Calcification	Yes	25 (61%)	42 (71.2%)	1.141[a]	0.286
	No	16 (39%)	17 (28.8%)		
Rim sign	Yes	5 (12.2%)	6 (10.2%)	.101[a]	0.750
	No	36 (87.8%)	53 (89.8%)		

Presence of ulceration (23.8 % v/s 23.7%) & calcification (61 % v/s 71.2%) in CT angiogram were noted in similar occurrence in asymptomatic and symptomatic carotids respectively.

. Majority had ICA stenosis in both the groups. IPH was noted to more prevalent in the symptomatic carotids.(36.4 v/s 48.4; (p value 0.44) . Symptomatic carotids had more prevalence of LRNC than asymptomatic carotids(79.3 v/s 43.2% ; p value 0.001).

Table 5- High risk plaque features in the study population.

		Groups		
		Asymptomatic	**Symptomatic**	P value
Side (L,R)	**L**	**20 (45.5%)**	**32 (55.2%)**	**0.331**
	R	**24 (54.5%)**	**26 (44.8%)**	
Total		**44 (100%)**	**58 (100%)**	
Intraplaque Hemorrhage	**Yes**	**16 (36.4%)**	**26 (44.8%)**	**0.440**
	No	**28 (63.6%)**	**31 (53.4%)**	
severity of stenosis	**50-69**	**17 (38.6%)**	**12 (20.7%)**	**0.047**
	>70	**27 (61.4%)**	**46 (79.3%)**	
Necrotic core	**Lipid rich**	**19 (43.2%)**	**46 (79.3%)**	**0.001**
	Fibrous rich	**11 (25%)**	**5 (8.6%)**	
	Calcium rich	**12 (27.3%)**	**5 (8.6%)**	
	Full IPH	**2 (4.5%)**	**0 (0%)**	
Fibrous Cap	Intact and smooth	19 (43.2%)	33 (56.9%)	52	0.265
	Ruptured	**23 (52.3%)**	**21 (36.2%)**	44	
Plaque Irregularity	**Yes**	**30 (68.2%)**	**38 (65.5%)**	68	0.308
	Smooth	14 (31.8%)	17 (29.3%)	31	
Neovascularisation	**Yes**	**19 (43.2%)**	**20 (34.5%)**	39	0.555
	No	24 (54.5%)	35 (60.3%)	59	
Ulceration	**Yes**	**19 (43.2%)**	**22 (37.9%)**	41	0.865

	No	23 (52.3%)	33 (56.9%)	56	
Mural Thrombus	Yes	0 (0%)	2 (5%)	2	0.322
	No	43 (97.7%)	37 (92.5%)	80	
Calcification	**Yes**	**27 (61.4%)**	**31 (54.4%)**	58	0.190
	No	17 (38.6%)	23 (40.4%)	40	
Modified American Heart association classification types	5-6	30 (68.2%)	45	75	0.116
	7-8	14 (31.8%)	10	24	
Total		44 (100%)	55	99	

The LRNC was more prevalent in the sCAS compared to aCAS. (79.3% v/s 43.2%; p value 0.001). Though not statistically significant, IPH was found to be more prevalent in the sCAS (48.4% v/s 36.4%; p=0.44).

There was no statistically significant difference in the prevalence of other HRPF: fibrous cap rupture, ulceration and plaque irregularity between sCAS and aCAS.

The presence of calcified plaque (27.3 v/s 8.6%; p – 0.19) was more prevalent in aCAS.

Chapter 6

Discussion



DISCUSSION

In this study, we compared the highrisk plaque features in symptomatic and asymptomatic carotid stenosis patients. We found that lipid rich necrotic core was the only feature that was statistically significant and more prevalent high risk plaque feature in symptomatic carotid artery stenosis.

IPH was found to be more prevalent in symptomatic carotids., however was not statistically significant.(figure 1, 2) IPH is the most validated imaging marker of high risk carotid plaque.,which occurs following an increase in lipid in the core, overproduction of free radicals and breakdown of core immature vessels. . A 2020 metaanalysis, found that the HR of IPH for recurrent stroke or TIA was 7.14 (95%CI, 4.32–11.82).[54] Our study also found IPH to be more common in symptomatic severe carotid stenosis (p- 0.048). IPH causes higher incidence of ipsilateral stroke and does not correlate with the severity of the luminal stenosis.One of the study showed that IPH can identify vulnerable plaques in mild to moderate stenosis too [57] Even in symptomatic patients with > 50 % stenosis, the absence of haemorrhage in a carotid plaque could suggest a benign course .[58]A recent meta-analysis found that IPH increased the risk of ipsilateral stroke in both asymptomatic (HR ¼ 7.9; 95% CI, 1.3–47.6) and symptomatic (HR ¼ 10.2; 95% CI, 4.6–22.5) patients, however the study didn't consider the grade of stenosis.[59]. A higher incidence of IPH was reported in patients without symptoms also.[60 -61, 2]. Most of the patients in our study underwent MR carotid plaque imaging atleast 2 weeks prior to endarterectomy. Its known that plaque process is a dynamic one and IPH may occur at any time in the course of a carotid plaque.[62-65]This is supported by studies which found IPH to be retained in 94- 97% plaques on follow up, which could be due to delayed clearance by macrophages.. Mostof the patients in our study were on statins after the first ischemic event. Till now we don't

have enough evidence to support the reduction of IPH by intense statin therapy. [40, 66-68] Hence it is likely that an IPH that has once occurred in a plaque may remain asymptomatic for long time. The mere presence of IPH hence will be less useful in differentiating symptomatic from asymptomatic plaques. This is especially true in greater degrees of luminal stenosis. [56]

The LRNC was more prevalent in the sCAS compared to aCAS. (79.3% v/s 43.2%; p value 0.001).(figure 3,4). A 2020 meta-analysis, found the hazard ratio (HR) of LRNC to be 2.73 (95% CI, 1.04–7.16) for recurrent stroke or TIA. [54] In addition, LRNCs can increase in size or be precursors of higher risk plaque features. [40.]We didn't not measure the volume of the lipid core in our patients. Studies have shown that after 3 years, the LRNC volume and the percentage of overall plaque volume can decrease by as much as 50%., no significant differences were found after 1– 6months [68]or 7–12months of therapy, but a significant decrease in LRNC volume was found after 1 year.[69,70]There is evidence that atherosclerosis can be reversed with high-dose lipid-lowering therapy, and may shift vulnerable plaque from high lipid content to a more stable calcified plaque. [71.] But once an IPH occurs in a plaque , it overrides the benefits of the statin therapy and becomes symptomatic. A change in plaque composition precede changes in plaque morphology. So baseline LRNC than IPH is more important in making a plaque vulnerable. Hence Baseline LRNC volume needs to be monitored in MR plaque imaging and a follow up scan , preferably at 6 [months68] . Most of the asymptomatic carotids in our study was calcium or fibrous rich,. It is possible that most patients were on statins following the event which could have stabilized the LRNC making them asymptomatic. However we could not demonstrate a change in LRNC volume with a follow up scan.

There was no statistically significant difference in the prevalence of other HRPF: fibrous cap rupture, ulceration and plaque irregularity between sCAS and aCAS. (figure 5,6,7). Studies have shown that larger and more stenotic plaques, with higher volumes of LRNC and/or IPH, and plaques with loss of fibrous cap integrity are more likely to develop ulcerations .[72, 74-75] .The prevalence of plaque rupture is more in symptomatic stenosis and has good histopathological correlation. [76, 15, 62] ·Plaque irregularity, ulceration and fibrous cap rupture, were common in asymptomatic carotids as in symptomatic in our study. In lesions with a new surface disruption, the percentage LRNC volume increased significantly faster compared with lesions with an intact surface(1.7_2.0% versus 0.1_0.7% per year, respectively; *P*_.049). [72]Plaques can have multiple ulcers and generally , one third heal after plaque rupture, [77-79 , 83] within 180 days after ischemia., which are mostly the proximal ulcers. However, there is no predictor of whether an ulcer will heal or not[80-81,82].,[84] Distal ulcers may not heal.[77-78.] Rather than the severity of stenosis, it's the volume of LRNC that predicts the risk of fibrous cap rupture[40.] . Around 1/3[rd] of the plaques in CTA were irregular,in our study amongst which only 1/3[rd] had ipsilateral chronic infarcts . However in 44 asymptomatic carotids 68% had plaque irregularity in plaque imaging, meaning that irregular plaques are not confined to symptomatic carotid stenosis.[84] Truly asymptomatic plaques also demonstrate inflammation but not to the extent of the contralateral asymptomatic stenosis when compared to the symptomatic side. , proving that inflammatory atheroma is a systemic disease. which is supported by the increased levels of MMP-2 and MMp-9 and cap rupture)p 0.010)[84]

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Our carotid plaque images were done in 3T , which offers better resolution[84]. The images were read by two independent radiologists who were blinded to the clinical and imaging data of the

patients. However our results were not statistically significant.The presence of ulcers which ruptured as a part of the generalized atherosclerotic disease , which later healed and remained asymptomatic can possibly explain our findings. However a bigger sample size and follow up scan for progression of the plaque & ischemic events is required in asymptomatic patients . Long-term preoperative administration of aspirin and use of heparin during surgery may explain the relatively low frequency of thrombosis observed in our study.

All irregular plaques may not be vulnerable enough to cause ischemic events[92- 93]. Plaque irregularity should be taken as a corroborative evidence of vulnerability. Today it is impossible to say whether each patient will progress through different stages of vulnerability. It is possible that asymptomatic patients will always be asymptomatic, and that symptomatic patients never had asymptomatic ruptures.

The presence of calcified plaque (27.3 v/s 8.6%; p – 0.19) was more prevalent in aCAS.Calcifications are found in up to 90% of atheromas. [86]. Multiple studies have shown that patients with large bulky calcified athero sclerotic plaques were more likely to be asymptomatic[87] . Plaque calcifications are a marker of plaque stability and found to less likely cause strokes[88, 89,91],.

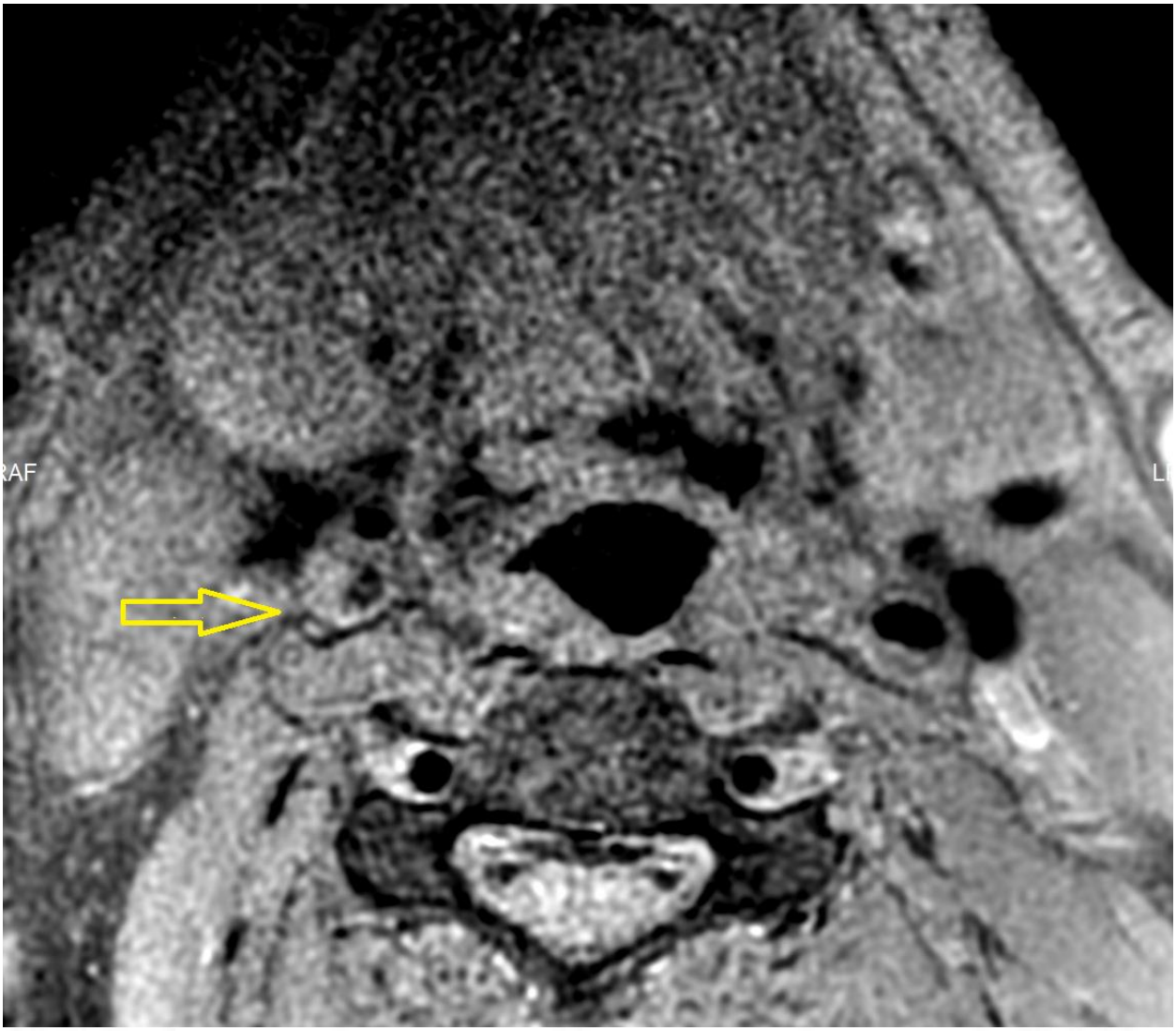


Figure 1- MR Carotid plaque imaging proton Density axial images showing intraplaque hemmorhage

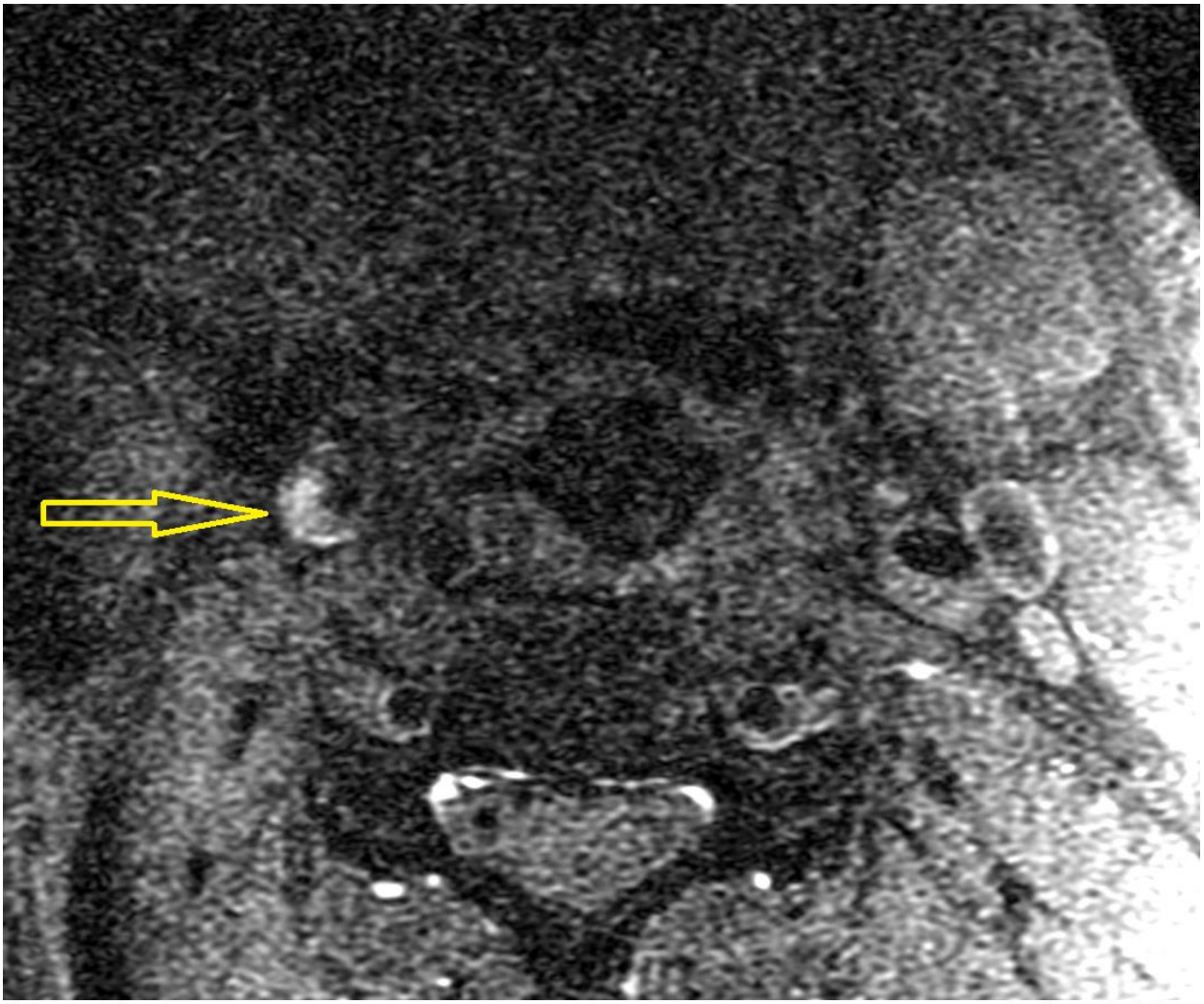


Figure 2- MR Carotid plaque imaging T1 fat suppressed axial images showing intraplaque hemorrhage

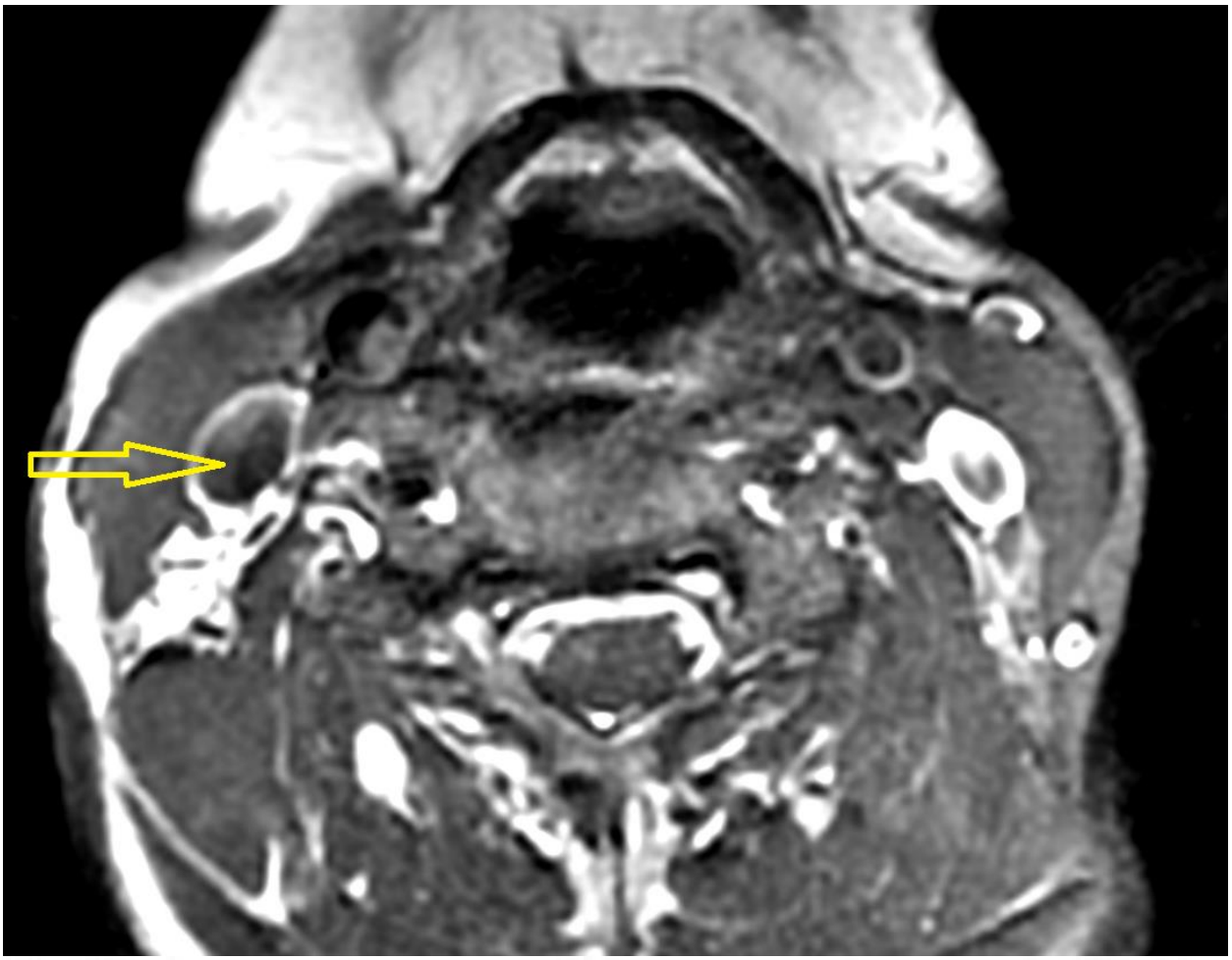


Figure 3- MR carotid plaque imaging T1 axial section showing lipid rich necrotic core

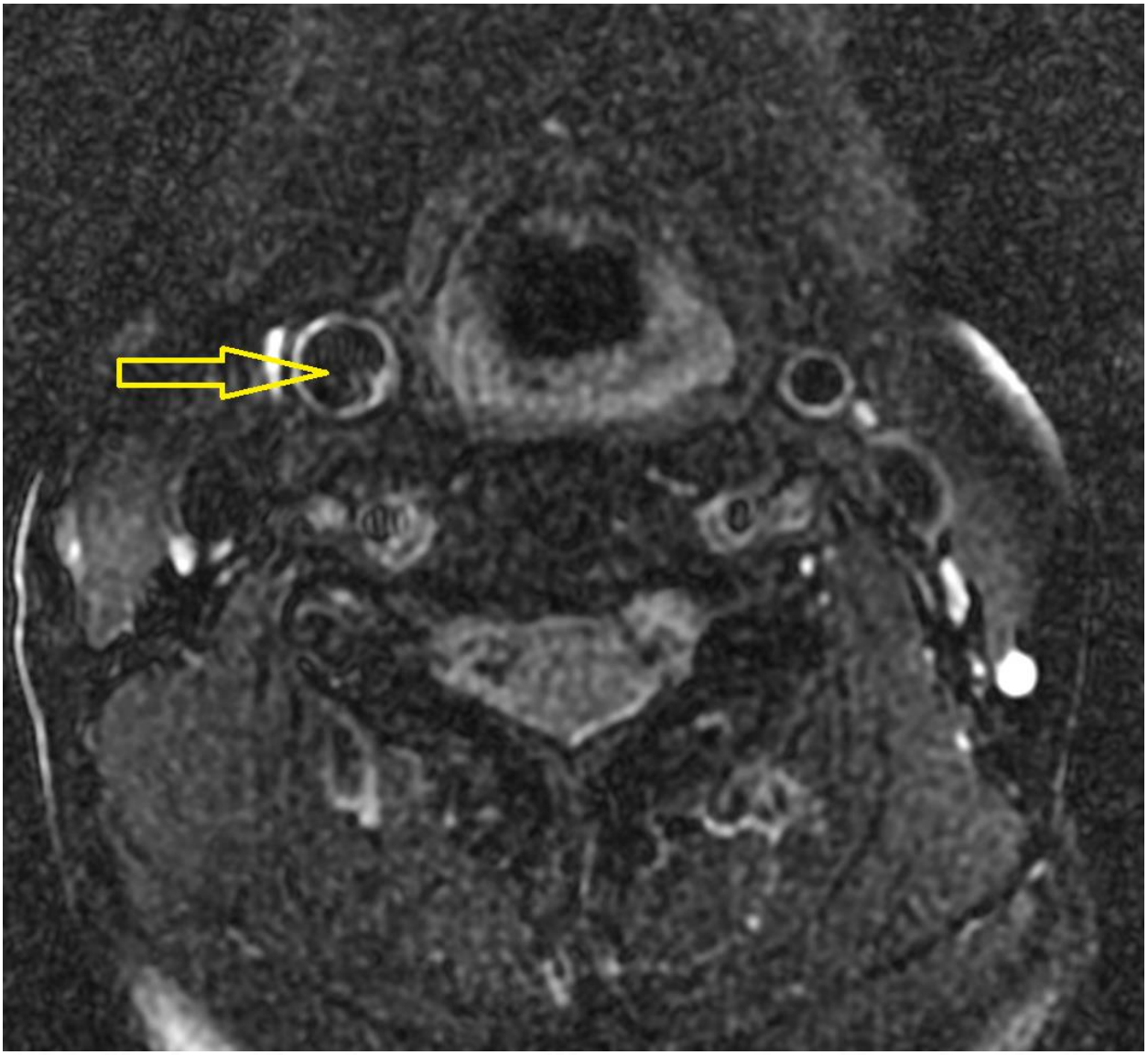


Figure 4- MR carotid plaque imaging T1 fat suppressed axial section showing non enhancement of lipid rich necrotic core

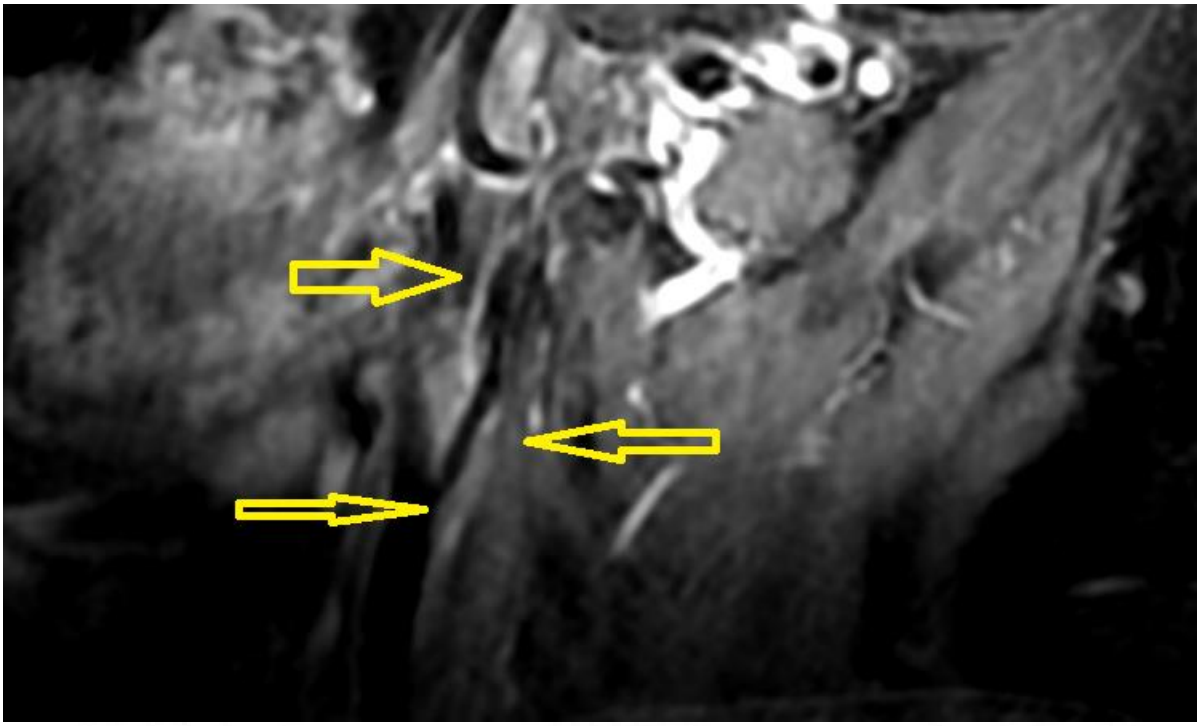


Figure 5- MR carotid plaque imaging T1 contrast sagittal section showing enhancement pattern suggestive of neovascularization

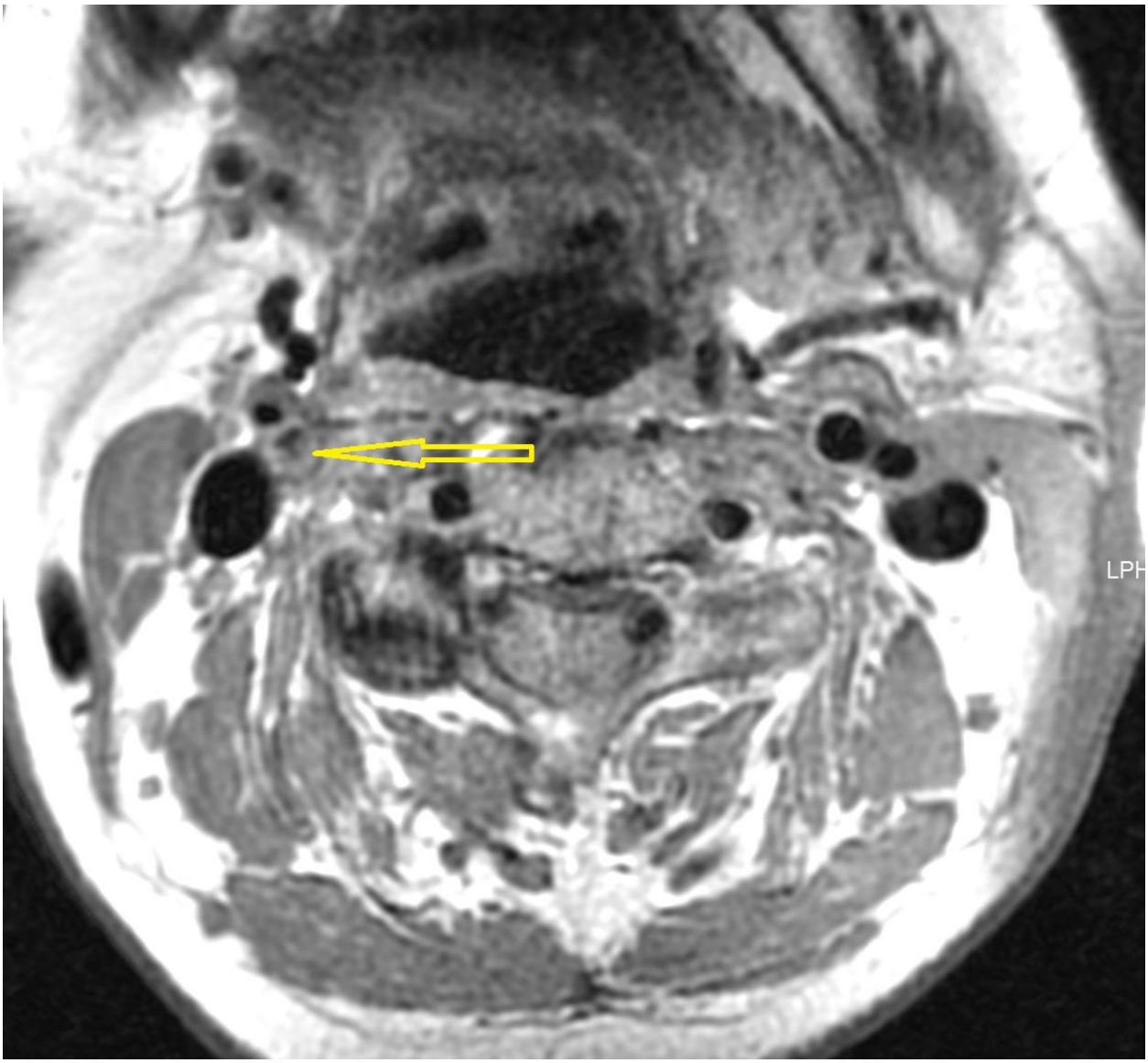


Figure 6- MR carotid plaque imaging T1 axial section showing ruptured fibrous cap.

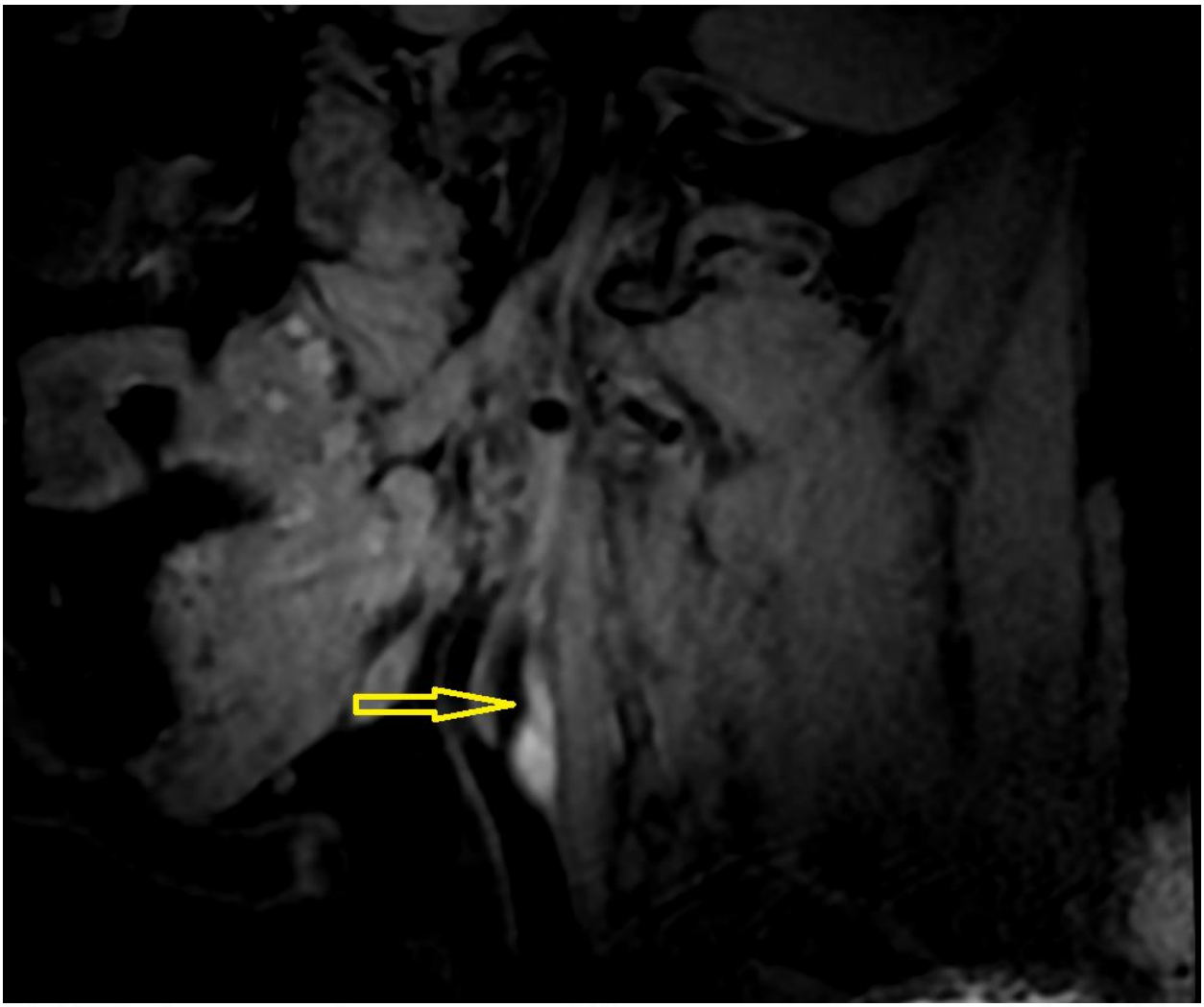


Figure 7- MR carotid plaque imaging T1 sagittal section showing ulceration of the plaque.

STRENGTHS

The strengths of the study include the prospective collection of data from both asymptomatic and symptomatic patients, utilization of 3 T MRI with contrast studies for carotid plaque imaging, with both radiologists being blinded to the clinical or other imaging data. We also tested the inter and intra observer variability which could influence the reliability of the carotid plaque imaging.

Chapter 7

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Conclusion



CONCLUSION

- Though IPH and LRNC were more prevalent in symptomatic carotid stenosis, HRPF was present in asymptomatic carotid stenosis also..
- Plaque ruptures can occur in asymptomatic carotid stenosis
- Plaque irregularity is not a definitive high risk feature in asymptomatic carotid stenosis and should be taken as corroborative evidence of plaque instability in asymptomatic carotids.
- MR plaque imaging may be of value in asymptomatic carotid stenosis and can contribute to decision making for carotid revascularization

Chapter 8

Limitations

LIMITATIONS

Our study should be interpreted with in context of its limitations.

As we used a dedicated carotid coil, we faced challenges such as: discomfort for obese patients with short necks, difficulty in keeping the carotid bifurcation in the iso center of the coils in such patients, to limit neck or swallowing movement in recovering stroke patients which caused movement artifacts.

Our study population predominantly had patients with both symptomatic and asymptomatic carotids, which could have confounding effect on the results.

Also, we couldn't follow up the asymptomatic patients for ischemic events.

We included only moderate and severe stenosis in both the groups, which could have lead to selection bias.

Chapter 9

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Chapter 10

ANNEXURES

ANNEXURE I: CASE PROFORMA

1. PERSONAL DETAILS

Patient number	
Medical record number	
Patient initials	
Age	
Gender	
Weight	
Postal address	
Contact number	

2. INCLUSION and EXCLUSION CRITERIA

INCLUSION CRITERIA	**YES**	**NO**
I. Presence of carotid stenosis ≥50%		
II. Baseline mRS ≤2		

EXCLUSION CRITERIA	**YES**	**NO**
I. Previous history of stroke/TIA in the same territory within 6 months		

II.	History of stroke due to another proven etiology like dissection, vasculitis		
III.	Patients with renal dysfunction		
IV.	Patients who have contraindications for MRI		

3. HISTORY OF RISK FACTORS

	RISK FACTORS	**YES**	**NO**
I.	Hypertension		
II.	Diabetes		
III.	Dyslipidemia		
IV.	Atrial fibrillation		
V.	Coronary Artery Disease		
VI.	Peripheral occlusive vascular disease		
VII.	Family history of stroke		
VIII.	Congestive heart failure		
IX.	Rheumatic heart disease		
X.	Chronic liver disease		
XI.	Chronic kidney disease		
XII.	Malignancy		

4. BEHAVIOURAL HISTORY

Behavioral history	Past	Current
I. Smoking		
II. Tobacco		
III. Alcohol		
IV. Any other addictions		

5. MEDICATION HISTORY

I. Oral hypoglycemic agents	
II. Antihypertensives	
III. Anticoagulants	
IV. Statins	

6. IMAGING DETAILS

CT BRAIN		
I. Any acute infarct	Yes	No
II. Any chronic infarct	Yes	No

If yes	Cortical	Sub cortical
III. Small vessel ischemic changes	Yes	No

CT ANGIOGRAM		
Findings	CCA	ICA
i. % of stenosis		
ii. Length of stenosis in mm		
iii. Plaque thickness		
iv. Ulceration (yes/no)		
v. Intraluminal thrombus (yes/no)		
vi. Rim sign (yes/no)		

MRI PLAQUE IMAGING		
Findings	Yes	No
i. Intraplaque hemorrhage		
ii. Lipid rich necrotic core		
iii. Thin / ruptured fibrous cap		
iv. Plaque irregularity		
v. Ulceration		
vi. Echolucency		
vii. Mural thrombus		
viii. Neovascularization		
ix. Plaque volume		
x. Juxta luminal hypoechoic area		

ANNEXURE III: IEC APPROVAL LETTER

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

CDSCO Registration No: ECR/189/Inst/KL/2013/RR-21
DHR Registration No:EC/NEW/INST/2022/2775

SCT/IEC/2216/MARCH/2024 15.04.2024

Dr. P.N. Sylaja
Professor and Head
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Sylaja,

The Institutional Ethics Committee held on 16th March, 2024, reviewed and discussed your application to conduct the study titled "**PREVALENCE OF HIGH RISK PLAQUE FEATURES IN ASYMPTOMATIC CAROTID ARTERY STENOSIS (IEC /2216)** "

Principal Investigator	Dr Sylaja. P.N, Professor and Head of Department, Neurology, SCTIMST
Co-Principal Investigator(s)	Dr Poornima Nair, PDF STROKE, Department of Neurology, SCTIMST
Co-Investigator(s)	Dr Sajith Sukumaran, Professor, Department of Neurology, SCTIMST Dr Sapna Erat Sreedharan, Professor, Department of Neurology, SCTIMST Dr Anoop A, Additional Professor, Department of Imaging Sciences and Interventional Radiology, SCTIMST
Duration of the study	8 months

The following members of the Ethics Committee were present at the meeting held on 16th March, 2024

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
5.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. Harikrishna Varma PR	Ph.D (Materials Science)	Male	Medical Technology	Yes
8.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
9.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
10.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
11.	Dr. Syam K	MBBS, MD, DM	Male	Clinician	Yes
12.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Responses/Amendments made based on the Reviewer's comments*
2. *Checklist Form*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 22.02.2024*
4. *Forwarding letter from HOD dated 22.02.2024*
5. *Study Proposal*
6. *IEC Application Form*
7. *Proforma*
8. *Patient/LAR Information Sheet in English and Malayalam*
9. *Participant Informed Consent Form in English and Malayalam*
10. *Declaration Form*
11. *CV of PI and Co-PIs*

Revised submission

1. *Checklist Form*
2. *Responses/Amendments made based on the Reviewer's comments*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 12.04.2024*
4. *Forwarding letter from HOD dated 12.04.2024*
5. *Study Proposal*
6. *IEC Application Form*
7. *Proforma*
8. *Patient/LAR Information Sheet in English and Malayalam*
9. *Participant Informed Consent Form in English and Malayalam*
10. *Declaration Form*
11. *CV of PI and Co-PIs*

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,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

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

ANNEXURE III- ABBREVIATIONS

ACAS	Asymptomatic carotid artery stenosis
ACES	Asymptomatic carotid Embolic study
ACST	Asymptomatic carotid artery stenosis trial
AHA	American Heart Association
BMT	Best Medical Management
CABG	Coronary artery bypass graft
CCA	Common Carotid artery
CEA	Carotid endarterectomy
CRP	C reactive protein
ICA	Internal carotid artery
ICU	Intensive care Unit
IPH	Intraplaque hemorrhage
LDL	Low density cholesterol
LRNC	Lipid rich necrotic core
MMP	Matrix metalloproteinases
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRS	Modified ranklin scale
NASCET	The North American Symptomatic Carotid Endarterectomy Trial
OPD	Outpatient department
PACS	Picture archiving and communication systems
PET	Positron emission tomography
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of Metalloproteinases
TOAST	Trial of Org10 172 in Acute Stroke Treatment
TOF	Time of flight